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(54) Title: COMBINATION OF EPOTHILONE ANALOGS AND CHEMOTHERAPEUTIC AGENTS FOR THE TREATMENT OF PROLIFERATIVE DISEASES

(57) Abstract: Compositions and methods are disclosed which are useful of the treatment and prevention of proliferative disorders.

## COMBINATION OF EPOTHILONE ANALOGS AND CHEMOTHERAPEUTIC AGENTS FOR THE TREATMENT OF PROLIFERATIVE DISEASES

**CROSS-REFERENCE TO RELATED APPLICATIONS**

5           This application claims priority from provisional  
application serial numbers 60/275,801, filed  
March 14, 2001 and 60/316,395, filed August 31, 2001,  
each incorporated herein by reference in its entirety.

10 FIELD OF THE INVENTION

This invention relates to the fields of oncology and improved chemotherapy regimens.

## BACKGROUND OF THE INVENTION

15       The disclosure of each literature article and  
published patent document referred to herein is  
incorporated by reference herein in its entirety.

The National Cancer Institute has estimated that in the United States alone, 1 in 3 people will be struck with cancer during their lifetime. Moreover, approximately 50% to 60% of people contracting cancer will eventually succumb to the disease. The widespread occurrence of this disease underscores the need for improved anticancer regimens for the treatment of malignancy.

Due to the wide variety of cancers presently observed, numerous anticancer agents have been developed to destroy cancer within the body. These compounds are administered to cancer patients with the objective of destroying or otherwise inhibiting the growth of malignant cells while leaving normal, healthy cells undisturbed. Anticancer agents have been classified based upon their mechanism of action.

One type of chemotherapeutic is referred to as a metal coordination complex. It is believed this type of chemotherapeutic forms predominantly inter-strand DNA cross links in the nuclei of cells, thereby preventing cellular replication. As a result, tumor growth is

initially repressed, and then reversed. Another type of chemotherapeutic is referred to as an alkylating agent. These compounds function by inserting foreign compositions or molecules into the DNA of dividing cancer  
5 cells. As a result of these foreign moieties, the normal functions of cancer cells are disrupted and proliferation is prevented. Another type of chemotherapeutic is an antineoplastic agent. This type of agent prevents, kills, or blocks the growth and spread of cancer cells. Still  
10 other types of anticancer agents include nonsteroidal aromatase inhibitors, bifunctional alkylating agents, etc.

Paclitaxel represents one of the major classes of antimicrotubule agents that promotes tubulin  
15 polymerization and, presumably, mitotic arrest during cell division. Taxol<sup>®</sup> (paclitaxel) has been shown to have excellent antitumor activity in vivo and has been employed in the treatment of a variety of cancers, including breast, ovarian and lung cancer.  
20 Unfortunately, many tumors develop resistance to paclitaxel.

The present inventors have discovered epothilone analogs that act synergistically when used in combination with certain conventional chemotherapeutic agents. It is  
25 an object of the invention to provide efficacious combination chemotherapeutic treatment regimens wherein epothilone analogs are combined with other anti-neoplastic agents for the treatment of proliferative diseases.

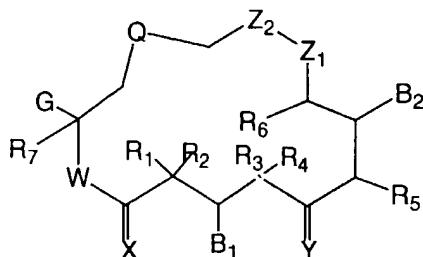
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#### SUMMARY OF THE INVENTION

The present invention provides a synergistic method for the treatment of anti-proliferative diseases, including cancer, which comprises administering to a  
35 mammalian specie in need thereof a synergistically,

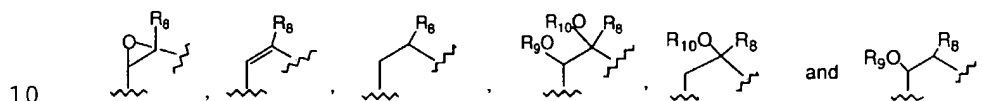
therapeutically effective amount of: (1) at least one anti-proliferative agent and (2) a compound of formula I wherein

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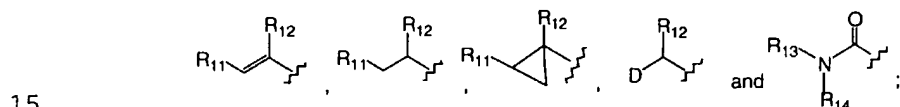


wherein:

Q is selected from the group consisting of



G is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo,



W is O or N R<sub>15</sub>;

X is O or H, H;

Y is selected from the group consisting of O; H, OR<sub>16</sub>; OR<sub>17</sub>, OR<sub>17</sub>; NOR<sub>18</sub>; H, NHOR<sub>19</sub>; H, NR<sub>20</sub>R<sub>21</sub>; H, H; and  
20 CHR<sub>22</sub>; wherein OR<sub>17</sub>, OR<sub>17</sub> can be a cyclic ketal;

Z<sub>1</sub> and Z<sub>2</sub> are independently selected from the group consisting of CH<sub>2</sub>, O, NR<sub>23</sub>, S, and SO<sub>2</sub>, wherein only one of Z<sub>1</sub> and Z<sub>2</sub> can be a heteroatom;

B<sub>1</sub> and B<sub>2</sub> are independently selected from the group consisting of OR<sub>24</sub>, OCOR<sub>25</sub>, and O-C(=O)-NR<sub>26</sub>R<sub>27</sub>, and when B<sub>1</sub> is H and Y is OH, H, they can form a six-membered ring ketal or acetal;

5 D is selected from the group consisting of NR<sub>28</sub>R<sub>29</sub>, NR<sub>30</sub>COR<sub>31</sub> and saturated heterocycle;

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>13</sub>, R<sub>14</sub>, R<sub>18</sub>, R<sub>19</sub>, R<sub>20</sub>, R<sub>21</sub>, R<sub>22</sub>, R<sub>26</sub> and R<sub>27</sub> are independently selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and  
10 when R<sub>1</sub> and R<sub>2</sub> are alkyl can be joined to form a cycloalkyl, and when R<sub>3</sub> and R<sub>4</sub> are alkyl can be joined to form a cycloalkyl;

R<sub>9</sub>, R<sub>10</sub>, R<sub>16</sub>, R<sub>17</sub>, R<sub>24</sub>, R<sub>25</sub> and R<sub>31</sub> are independently selected from the group consisting of H, alkyl, and  
15 substituted alkyl;

R<sub>8</sub>, R<sub>11</sub>, R<sub>12</sub>, R<sub>28</sub>, R<sub>30</sub>, R<sub>32</sub>, and R<sub>33</sub> are independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl and heterocyclo;

20 R<sub>15</sub>, R<sub>23</sub> and R<sub>29</sub> are independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo, R<sub>32</sub>C=O, R<sub>33</sub>SO<sub>2</sub>, hydroxy, O-alkyl or O-substituted alkyl; and

pharmaceutically acceptable salts thereof and any  
25 hydrates, solvates or geometric, optical and stereoisomers thereof;

with the proviso that compounds wherein

W and X are both O; and

R<sub>1</sub>, R<sub>2</sub> and R<sub>7</sub> are H; and

30 R<sub>3</sub>, R<sub>4</sub> and R<sub>6</sub> are methyl; and

R<sub>8</sub> is H or methyl; and

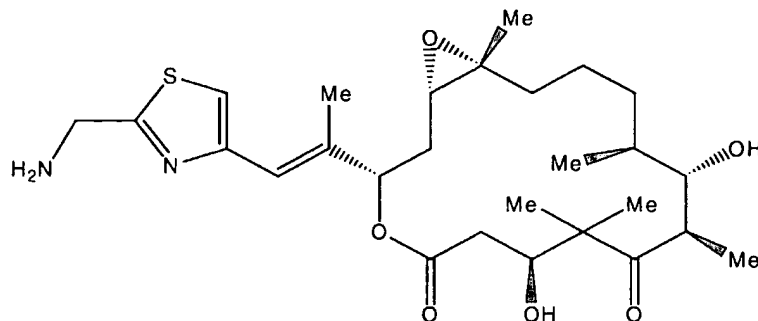
Z<sub>1</sub> and Z<sub>2</sub> are CH<sub>2</sub>; and

G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl;

and

Q is as defined above.  
are excluded.

Formula II provides another example of an epothilone  
suitable for use in the methods and compositions of the  
present invention:

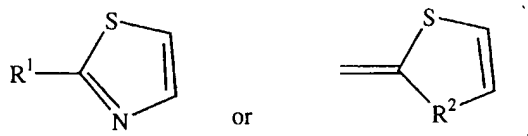


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where:

P-Q is a C, C double bond or an epoxide;

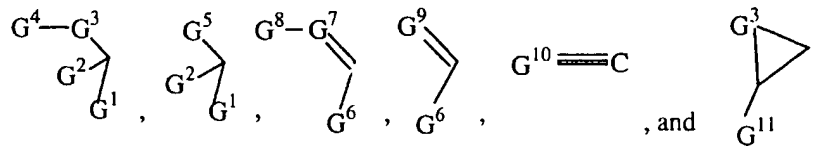
G is



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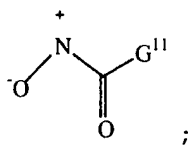
R is selected from the group of H, alkyl, and  
substituted alkyl;

R<sup>1</sup> is selected from the group consisting of



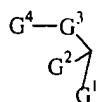
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R<sup>2</sup> is



- $G^1$  is selected from the group of H, halogen, CN, alkyl and substituted alkyl;
- $G^2$  is selected from the group of H, alkyl, and substituted alkyl;
- 5  $G^3$  is selected from the group of O, S, and  $NZ^1$ ;
- $G^4$  is selected from the group of H, alkyl, substituted alkyl,  $OZ^2$ ,  $NZ^2Z^3$ ,  $Z^2C=O$ ,  $Z^4SO_2$ , and optionally substituted glycosyl;
- $G^5$  is selected from the group of halogen,  $N_3$ , NCS, SH, CN, NC,  $N(Z^1)_3^+$  and heteroaryl;
- 10  $G^6$  is selected from the group of H, alkyl, substituted alkyl,  $CF_3$ ,  $OZ^5$ ,  $SZ^5$ , and  $NZ^5Z^6$ ;
- $G^7$  is  $CZ^7$  or N;
- $G^8$  is selected from the group of H, halogen, alkyl, substituted alkyl,  $OZ^{10}$ ,  $SZ^{10}$ ,  $NZ^{10}Z^{11}$ ;
- 15  $G^9$  is selected from the group of O, S, -NH-NH- and -N=N-;
- $G^{10}$  is N or  $CZ^{12}$ ;
- $G^{11}$  is selected from the group of  $H_2N$ , substituted  $H_2N$ , alkyl, substituted alkyl, aryl, and substituted aryl;
- 20  $Z^1$ ,  $Z^6$ ,  $Z^9$ , and  $Z^{11}$  are independently selected from the group H, alkyl, substituted alkyl, acyl, and substituted acyl;
- $Z^2$  is selected from the group of H, alkyl, substituted alkyl, aryl, substituted aryl, and heterocycle;
- 25  $Z^3$ ,  $Z^5$ ,  $Z^8$ , and  $Z^{10}$  are independently selected from the group H, alkyl, substituted alkyl, acyl, substituted acyl, aryl, and substituted aryl;
- 30  $Z^4$  is selected from the group of alkyl, substituted alkyl, aryl, substituted aryl, and heterocycle;
- $Z^7$  is selected from the group of H, halogen, alkyl, substituted alkyl, aryl, substituted aryl,  $OZ^8$ ,  $SZ^8$ , and  $NZ^8Z^9$ ; and
- 35  $Z^{12}$  is selected from the group of H, halogen, alkyl,

substituted alkyl, aryl, and substituted aryl;  
with the proviso that when  $R^1$  is

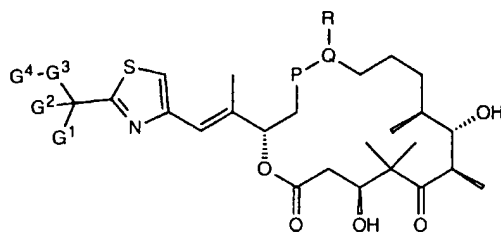


$G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  cannot simultaneously have the  
5 following meanings:

$G^1$  and  $G^2 = H$ ,  $G^3 = O$  and  $G^4 = H$  or  $Z^2C=O$  where  $Z^2 =$   
alkyl group.

A preferred compound of Formula II of the invention is  
Formula IIa

10



15

where the symbols have the following meaning:

P-Q is a C,C double bond or an epoxide,

R is a H atom or a methyl group,

$G^1$  is an H atom, an alkyl group, a substituted alkyl group  
20 or a halogen atom,

$G^2$  is an H atom, an alkyl group or a substituted alkyl  
group,

$G^3$  is an O atom, an S atom or an  $NZ^1$  group with  
 $Z^1$  being an H atom, an alkyl group, a substituted alkyl

25 group, an acyl group, or a substituted acyl group, and

$G^4$  is an H atom, an alkyl group, a substituted alkyl  
group, an  $OZ^2$  group, an  $NZ^2Z^3$  group, a  $Z^2C=O$  group, a  $Z^4SO_2$   
group or an optionally substituted glycosyl group with  $Z^2$



being a H atom, an alkyl group, a substituted alkyl group, an aryl group, a substituted aryl group or a heterocyclic group,

5  $Z^3$  an H atom, an alkyl group, a substituted alkyl group, an acyl group or a substituted acyl group, and  $Z^4$  an alkyl, a substituted alkyl, an aryl, a substituted aryl or a heterocyclic group, with the proviso that  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  cannot have simultaneously the following meanings:  $G^1$  and  $G^2$  = H atom,  $G^3$  = O atom and  $G^4$  = H atom or  
10  $Z^2C=O$  with  $Z^2$  = alkyl group.

A particularly preferred compound of Formula II is  
[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-  
15 dioxabicyclo[14.1.0]heptadecane-5,9-dione (Compound 4)  
and pharmaceutically acceptable salts thereof.

Suitable anti-proliferative agents for use in the methods of the invention, include, without limitation, alkylating agents (including, without limitation,  
20 nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes): Uracil mustard, Chlormethine, Cyclophosphamide (Cytosan®), Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylene-melamine, Triethylenethiophosphoramine, Busulfan,  
25 Carmustine, Lomustine, Streptozocin, Dacarbazine, and Temozolomide; antimetabolites (including, without limitation, folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors), Methotrexate, 5-Fluorouracil, Floxuridine, Cytarabine, 6-  
30 Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, Pentostatine, and Gemcitabine; natural products and their derivatives (for example, vinca alkaloids, antitumor antibiotics, enzymes, lymphokines and epipodophyllotoxins): Vinblastine, Vincristine,  
35 Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Ara-C, paclitaxel

(paclitaxel is commercially available as Taxol®),  
Mithramycin, Deoxyco-formycin, Mitomycin-C, L-  
Asparaginase, Interferons (especially IFN-a), Etoposide,  
and Teniposide; navelbene, CPT-11, anastrozole,  
5 letrozole, capecitabine, reloxafine, cyclophosphamide,  
ifosamide, and droloxafine and radiation.

The present invention further provides a  
pharmaceutical composition for the synergistic treatment  
of cancer which comprises at least one anti-proliferative  
10 agent, and a compound of Formulas I and/or II, and a  
pharmaceutically acceptable carrier.

In a preferred embodiment of the invention the  
antiproliferative agent is administered simultaneous with  
or before or after the administration of a compound of  
15 Formulas I and/or II.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the cytotoxicity spectrum of  
Compound 1 versus a panel of tumor cell lines in an  
20 Oncology Diverse Cell Assay. Bar graphs, on the right,  
depict the IC<sub>50</sub> values of the cell lines listed on the  
left hand column (top to bottom).

Figure 2 shows a time course of the mitotic  
25 blockade induced by incubation of HCT116 cells in the  
presence of 7.5 nM Compound 1.

Figures 3A and 3B are a pair of graphs showing  
the synergism with combination chemotherapy using  
30 Compound 2 and Compound 1. Synergism was obtained at a  
range of Compound 1 and Compound 2 concentrations and  
appeared not to be dependent on a particular  
concentration of each agent used in the combination. In  
the case of Compound 2, concentrations of 0.33  $\mu$ M (Fig.  
35 3A) and 0.11  $\mu$ M (FIG. 3B) all produced synergistic

interaction with various concentrations of Compound 1. In these experiments, Compound 1 was given first for 20 hr followed by Compound 2 for a second 20 hr period of treatment.

5

Figure 4 is a graph showing the comparative anti-tumor activity of Compound 1 and paclitaxel against a scPat-7 human ovarian cancer carcinoma model.

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Figure 5 is a graph showing the comparative anti-tumor activity of oral administration of Compound 1 and intravenous administration of paclitaxel in the Pat-7 human ovarian carcinoma model.

15

Figure 6 is a graph showing the dependency of compound 1 anti-tumor activity on treatment schedule in the A2780 human ovarian cancer model.

20

Figure 7 is a graph demonstrating the therapeutic synergism *in vivo* in multidrug-resistant human tumor xenografts (HCTVM46 human colon carcinoma) grown in nude mice following combination chemotherapy using Compound 2 and Compound 1. Compound 1 was administered iv 24 hr preceding the administration Compound 2 ip. Data shown were maximum tolerated regimens: Compound 1 alone (15 mg/kg, q4dx3), Compound 2 alone (400 mg/kg, q4dx3), combination (Compound 1 at 6 mg/kg followed by Compound 2 at 400 mg/kg).

25

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Figure 8 demonstrates the schedule dependency of combining Compound 1 and Compound 2 *in vivo* against a multidrug-resistant human tumor xenografts (HCTVM46 human colon carcinoma) grown in nude mice. In contrast to other reported schedules described above, administration of Compound 2 one day before Compound 1 did not result in

35

therapeutic synergism. Data shown were maximum tolerated regimens: Compound 1 alone (10 mg/kg, iv, q4dx3), Compound 2 alone (400 mg/kg, ip, q4dx3), combination (Compound 2 at 300 mg/kg followed by Compound 1 at 10 mg/kg).

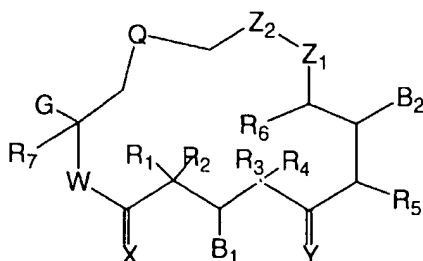
#### DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, methods for the scheduled administration of epothilone analogs in synergistic combination(s) with at least one additional anti-neoplastic agent for the treatment and prevention of proliferative diseases are provided.

Epothilones mimic the biological effects of taxol, (Bollag et al., Cancer Research 55: 2325-2333 (1995), and in competition studies act as competitive inhibitors of taxol binding to microtubules. However, epothilones enjoy a significant advantage over taxol in that epothilones exhibit a much lower drop in potency compared to taxol against a multiple drug-resistant cell line (Bollag et al. (1995)). Furthermore, epothilones are considerably less efficiently exported from the cells by P-glycoprotein than is taxol (Gerth et al. (1996)).

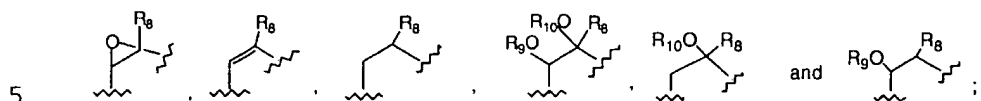
Thus, in a preferred embodiment, the chemotherapeutic method of the invention comprises the administration of epothilone analog of Formulas I and/or II in combination with other anti-cancer agents. The epothilone analogs disclosed herein, when used in combination with at least one other anti-cancer agent(s) demonstrate superior cytotoxic activity.

A preferred epothilone analog for use in the methods of the invention is a compound of Formula I wherein

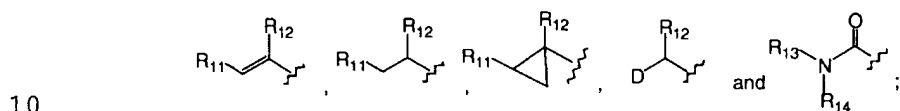


wherein:

Q is selected from the group consisting of



G is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo,



W is 0 or N  $R_{15}$ ;

X is 0 or H, H;

Y is selected from the group consisting of O; H, OR<sub>16</sub>; OR<sub>17</sub>, OR<sub>17</sub>; NOR<sub>18</sub>; H, NHOR<sub>19</sub>; H, NR<sub>20</sub>R<sub>21</sub>; H, H; and CHR<sub>22</sub>; wherein OR<sub>17</sub>, OR<sub>17</sub> can be a cyclic ketal;

Z<sub>1</sub> and Z<sub>2</sub> are independently selected from the group consisting of CH<sub>2</sub>, O, NR<sub>23</sub>, S, and SO<sub>2</sub>, wherein only one of Z<sub>1</sub> and Z<sub>2</sub> can be a heteroatom;

B<sub>1</sub> and B<sub>2</sub> are independently selected from the group consisting of OR<sub>24</sub>, OCOR<sub>25</sub>, and O-C(=O)-NR<sub>26</sub>R<sub>27</sub>, and when B<sub>1</sub> is H and Y is OH, H, they can form a six-membered ring ketal or acetal;

D is selected from the group consisting of  $\text{NR}_{28}\text{R}_{29}$ ,  $\text{NR}_{30}\text{COR}_{31}$  and saturated heterocycle;

25 R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>13</sub>, R<sub>14</sub>, R<sub>18</sub>, R<sub>19</sub>, R<sub>20</sub>, R<sub>21</sub>,  
R<sub>22</sub>, R<sub>26</sub> and R<sub>27</sub> are independently selected from the group  
consisting of H, alkyl, substituted alkyl, and aryl, and

when R<sub>1</sub> and R<sub>2</sub> are alkyl can be joined to form a cycloalkyl, and when R<sub>3</sub> and R<sub>4</sub> are alkyl can be joined to form a cycloalkyl;

5 R<sub>9</sub>, R<sub>10</sub>, R<sub>16</sub>, R<sub>17</sub>, R<sub>24</sub>, R<sub>25</sub> and R<sub>31</sub> are independently selected from the group consisting of H, alkyl, and substituted alkyl;

10 R<sub>8</sub>, R<sub>11</sub>, R<sub>12</sub>, R<sub>28</sub>, R<sub>30</sub>, R<sub>32</sub>, and R<sub>33</sub> are independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl and heterocyclo;

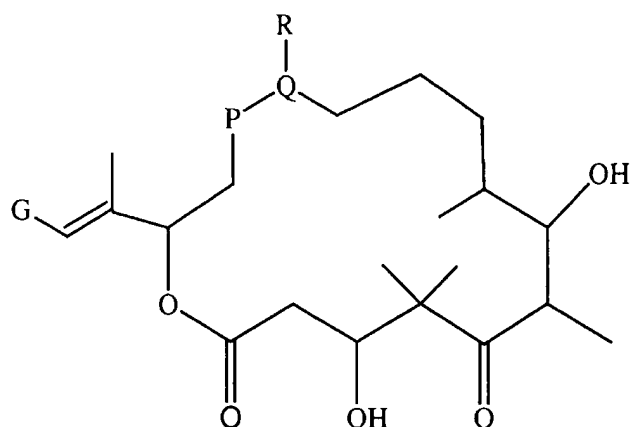
R<sub>15</sub>, R<sub>23</sub> and R<sub>29</sub> are independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo, R<sub>32</sub>C=O, R<sub>33</sub>SO<sub>2</sub>, hydroxy, O-alkyl or O-substituted alkyl; and  
15 pharmaceutically acceptable salts thereof and any hydrates, solvates or geometric, optical and stereoisomers thereof;

with the proviso that compounds wherein  
W and X are both O; and  
20 R<sub>1</sub>, R<sub>2</sub> and R<sub>7</sub> are H; and  
R<sub>3</sub>, R<sub>4</sub> and R<sub>6</sub> are methyl; and  
R<sub>8</sub> is H or methyl; and  
Z<sub>1</sub> and Z<sub>2</sub> are CH<sub>2</sub>; and  
G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl;  
25 and

Q is as defined above  
are excluded.

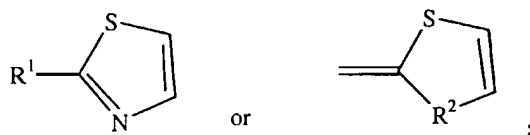
Another preferred epothilone for use in the present invention is a compound of Formula II:

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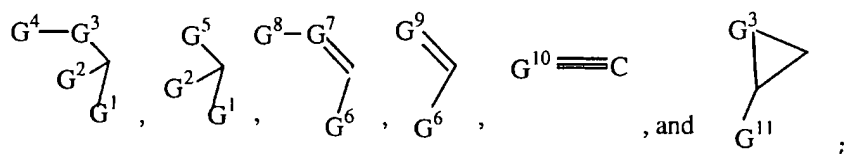
wherein:

- 5           P-Q is a C, C double bond or an epoxide;  
           G is

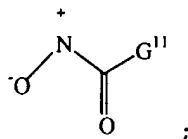


R is selected from the group of H, alkyl, and substituted alkyl;

- 10          R¹ is selected from the group consisting of



R² is



- 15          G¹ is selected from the group of H, halogen, CN, alkyl and substituted alkyl;  
           G² is selected from the group of H, alkyl, and substituted alkyl;  
           G³ is selected from the group of O, S, and NZ¹;

$G^4$  is selected from the group of H, alkyl, substituted alkyl,  $OZ^2$ ,  $NZ^2Z^3$ ,  $Z^2C=O$ ,  $Z^4SO_2$ , and optionally substituted glycosyl;

$G^5$  is selected from the group of halogen,  $N_3$ , NCS, SH, CN, NC,  $N(Z^1)_3^+$  and heteroaryl;

$G^6$  is selected from the group of H, alkyl, substituted alkyl,  $CF_3$ ,  $OZ^5$ ,  $SZ^5$ , and  $NZ^5Z^6$ ;

$G^7$  is  $CZ^7$  or N;

$G^8$  is selected from the group of H, halogen, alkyl, substituted alkyl,  $OZ^{10}$ ,  $SZ^{10}$ ,  $NZ^{10}Z^{11}$ ;

$G^9$  is selected from the group of O, S,  $-NH-NH-$  and  $-N=N-$ ;

$G^{10}$  is N or  $CZ^{12}$ ;

$G^{11}$  is selected from the group of  $H_2N$ , substituted  $H_2N$ , alkyl, substituted alkyl, aryl, and substituted aryl;

$Z^1$ ,  $Z^6$ ,  $Z^9$ , and  $Z^{11}$  are independently selected from the group H, alkyl, substituted alkyl, acyl, and substituted acyl;

$Z^2$  is selected from the group of H, alkyl, substituted alkyl, aryl, substituted aryl, and heterocycle;

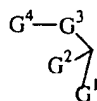
$Z^3$ ,  $Z^5$ ,  $Z^8$ , and  $Z^{10}$  are independently selected from the group H, alkyl, substituted alkyl, acyl, substituted acyl, aryl, and substituted aryl;

$Z^4$  is selected from the group of alkyl, substituted alkyl, aryl, substituted aryl, and heterocycle;

$Z^7$  is selected from the group of H, halogen, alkyl, substituted alkyl, aryl, substituted aryl,  $OZ^8$ ,  $SZ^8$ , and  $NZ^8Z^9$ ; and

$Z^{12}$  is selected from the group of H, halogen, alkyl, substituted alkyl, aryl, and substituted aryl;

with the proviso that when  $R^1$  is

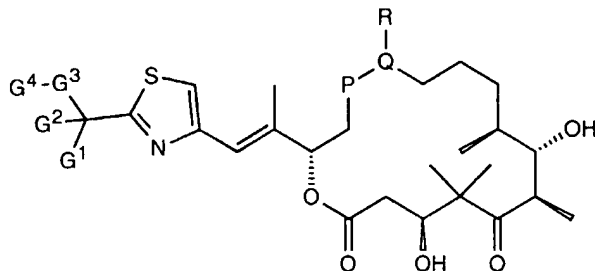




$G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  cannot simultaneously have the following meanings:

$G^1$  and  $G^2 = H$ ,  $G^3 = O$  and  $G^4 = H$  or  $Z^2C=O$  where  $Z^2 =$  alkyl group.

- 5 A preferred compound of Formula II of the invention is Formula Iia:



- 10 where the symbols have the following meaning:

P-Q is a C,C double bond or an epoxide,

R is a H atom or a methyl group,

$G^1$  is an H atom, an alkyl group, a substituted alkyl group or a halogen atom,

- 15  $G^2$  is an H atom, an alkyl group or a substituted alkyl group,

$G^3$  is an O atom, an S atom or an  $NZ^1$  group with  $Z^1$  being an H atom, an alkyl group, a substituted alkyl group, an acyl group, or a substituted acyl group, and

- 20  $G^4$  is an H atom, an alkyl group, a substituted alkyl group, an  $OZ^2$  group, an  $NZ^2Z^3$  group, a  $Z^2C=O$  group, a  $Z^4SO_2$  group or an optionally substituted glycosyl group with  $Z^2$  being a H atom, an alkyl group, a substituted alkyl group, an aryl group, a substituted aryl group or a

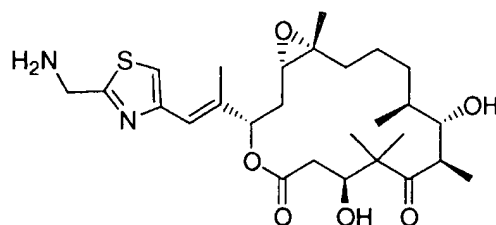
- 25 heterocyclic group,

$Z^3$  an H atom, an alkyl group, a substituted alkyl group, an acyl group or a substituted acyl group, and

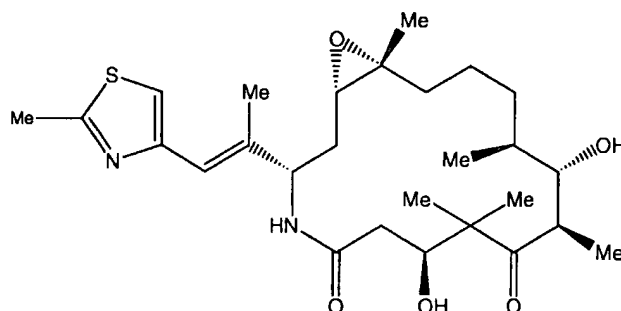
$Z^4$  an alkyl, a substituted alkyl, an aryl, a substituted aryl or a heterocyclic group, with the proviso that  $G^1$ ,

$G^2$ ,  $G^3$  and  $G^4$  cannot have simultaneously the following meanings:  $G^1$  and  $G^2$  = H atom,  $G^3$  = O atom and  $G^4$  = H atom or  $Z^2C=O$  with  $Z^2$  = alkyl group.

A further preferred compound of Formula II is  
 5 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (Compound 4) and pharmaceutically acceptable salts thereof. This  
 10 preferred compound (Compound 4) is of formula:



15 A preferred compound of Formula I is [1S 1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*, 16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17oxabicyclo[14.1.0]-heptadecane-5,9-dione (Compound 1) and pharmaceutically  
 20 acceptable salts thereof. This preferred compound (Compound 1) is of formula:



When describing the compounds of the present invention, the phrase "lower alkyl" or "lower alk" (as part of another group) refers to an unsubstituted alkyl group of 1 to 6, preferably 1 to 4, carbon atoms.

5       The term "aralkyl" refers to an aryl group bonded directly through a lower alkyl group. A preferred aralkyl group is benzyl.

      The term "aryl" refers to a monocyclic or bicyclic aromatic hydrocarbon group having 6 to 12 carbon atoms in  
10   the ring portion. Exemplary of aryl herein are phenyl, naphthyl and biphenyl groups.

      The term "heterocyclo" refers to a fully saturated or unsaturated, aromatic or nonaromatic cyclic group which is a 4 to 7 membered monocyclic, 7 to 11 membered  
15   bicyclic, or 10 to 15 membered tricyclic ring system which has at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4  
      heteroatoms selected from nitrogen, oxygen and sulfur  
20   where the nitrogen and sulfur heteroatoms may also optionally be oxidized and the nitrogen heteroatoms may also optionally be quaternized. The heterocyclo group may be attached at any heteroatom or carbon atom.

      Exemplary monocyclic heterocyclo groups include  
25   pyrrolidinyl, pyrrolyl, indolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl,  
30   oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxazepinyl, azepinyl, 4-piperidonyl, pyridyl, N-oxo-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydrothiopyranyl, tetrahydropyranyl, morpholinyl,  
35   thiamorpholinyl, thiamorpholinyl sulfoxide,

tetrahydrothiopyranylsulfone, thiamorpholinyl sulfone, 1,3-dioxolane, tetrahydro-1,1-dioxothienyl, dioxanyl, isothiazolidinyl, thietanyl, thiiranyl, triazinyl, triazolyl, and the like.

- 5 Exemplary bicyclic heterocyclo groups include benzothiazolyl, benzoxazolyl, benzothienyl, quinolinyl, quinolinyl-N-oxide, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, cinnolinyl,
- 10 quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,1-b]pyridinyl or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), benzisothiazolyl, benzisoxazolyl,
- 15 benzodiazinyl, benzofurazanyl, benzothiopyranyl, benzotriazolyl, benzpyrazolyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydrobenzopyranyl, indolinyl, isochromanyl, isoindolinyl, naphthyridinyl,
- 20 phthalazinyl, piperonyl, purinyl, pyridopyridyl, quinazolinyl, tetrahydroquinolinyl, thienofuryl, thienopyridyl, thienothienyl, and the like.

- When a group is referred to as being optionally substituted, it may be substituted with one to five,
- 25 preferably one to three, substituents such as F, Cl, Br, I, trifluoromethyl, trifluoromethoxy, hydroxy, lower alkoxy, cycloalkoxy, heterocyclooxy, oxo, lower alkanoyl, aryloxy, lower alkanoyloxy, amino, lower alkylamino, arylamino, aralkylamino, cycloalkylamino,
- 30 heterocycloamino, disubstituted amines in which the two amino substituents independently are selected from lower alkyl, aryl or aralkyl, lower alkanoylamino, aroylamino, aralkanoylamino, substituted lower alkanoylamino, substituted arylamino, substituted aralkylanoylamino,
- 35 thiol, lower alkylthio, arylthio, aralkylthio,

cycloalkylthio, heterocyclothio, lower alkylthiono, arylthiono, aralkylthiono, lower alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamide (e.g.,  $\text{SO}_2\text{NH}_2$ ), substituted sulfonamide, nitro, cyano, carboxy, carbamyl  
5 (e.g.,  $\text{CONH}_2$ ), substituted carbamyl (e.g.,  $\text{CONH}$ -lower alkyl,  $\text{CONH}$ -aryl,  $\text{CONH}$ -aralkyl or cases where there are two substituents on the nitrogen independently selected from lower alkyl, aryl or aralkyl), lower alkoxycarbonyl, aryl, substituted aryl, guanidino, and heterocyclos  
10 (e.g., indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like). Where noted above that the substituent is further substituted, it will be substituted with F, Cl, Br, I, optionally substituted lower alkyl, hydroxy, optionally substituted  
15 lower alkoxy, optionally substituted aryl, or optionally substituted aralkyl.

All stereoisomers of the Formula I and II compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The  
20 definition of the formula I compounds embraces all possible stereoisomers and their mixtures. The Formula I and II definitions very particularly embrace the racemic forms and the isolated optical isomers having the specified activity.

25 A particularly preferred epothilone analog for use in the methods of the invention is Compound 1: [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]  
30 heptadecane-5,9-dione. Another preferred epothilone is Compound 4: [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.

Compound 1, an exemplary epothilone analog of the invention, is a semi-synthetic epothilone analog and has a mode of action analogous to paclitaxel (i.e., microtubule stabilization). However, in preclinical pharmacology studies, Compound 1 has demonstrated significant improvement over paclitaxel in several critical aspects. Compound 1 exhibits a very impressive and broad spectrum of antitumor activity against paclitaxel-sensitive (A2780, HCT116 and LS174T) and, more importantly, as well as paclitaxel-resistant human colon tumors (HCT116/VM46), ovarian carcinoma (Pat-7 and A2780Tax) and breast carcinoma (Pat-21) models. Compound 1 is orally efficacious; the antitumor activity produced after oral administration is comparable to that produced by parenteral administration of the drug. These preclinical efficacy data indicate that Compound 1 demonstrates improved clinical efficacy in TAXOL®-insensitive and sensitive disease types.

In a preferred embodiment of the invention a compound of Formulas I and/or II is administered in conjunction with at least one anti-neoplastic agent.

As used herein, the phrase "anti-neoplastic agent" is synonymous with "chemotherapeutic agent" and/or "anti-proliferative agent" and refers to compounds that prevent cancer, or hyperproliferative cells from multiplying. Anti-proliferative agents prevent cancer cells from multiplying by: (1) interfering with the cell's ability to replicate DNA and (2) inducing cell death and/or apoptosis in the cancer cells.

Classes of compounds that may be used as anti-proliferative cytotoxic agents include the following:

Alkylating agents (including, without limitation, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes): Uracil mustard, Chloromethine, Cyclophosphamide (Cytoxan®), Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylene-

melamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, and Temozolomide.

Antimetabolites (including, without limitation,  
5 folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors): Methotrexate, 5-Fluorouracil, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, Pentostatine, and Gemcitabine.

10 Natural products and their derivatives (for example, vinca alkaloids, antitumor antibiotics, enzymes, lymphokines and epipodophyllotoxins): Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Ara-C,  
15 paclitaxel (paclitaxel is commercially available as Taxol®), Mithramycin, Deoxyco-formycin, Mitomycin-C, L-Asparaginase, Interferons (especially IFN-a), Etoposide, and Teniposide.

Other anti-proliferative cytotoxic agents are  
20 navelbene, CPT-11, anastrozole, letrozole, capecitabine, reloxafine, cyclophosphamide, ifosamide, and droloxafine.

The phrase "radiation therapy" includes, but is not limited to, x-rays or gamma rays which are delivered from either an externally applied source such as a beam or by  
25 implantation of small radioactive sources

Microtubule affecting agents interfere with cellular mitosis and are well known in the art for their anti-proliferative cytotoxic activity. Microtubule affecting agents useful in the invention include, but are not  
30 limited to, allocolchicine (NSC 406042), Halichondrin B (NSC 609395), colchicine (NSC 757), colchicine derivatives (e.g., NSC 33410), dolastatin 10 (NSC 376128), maytansine (NSC 153858), rhizoxin (NSC 332598), paclitaxel (Taxol®, NSC 125973), Taxol® derivatives

- (e.g., derivatives (e.g., NSC 608832), thiocolchicine NSC 361792), trityl cysteine (NSC 83265), vinblastine sulfate (NSC 49842), vincristine sulfate (NSC 67574), natural and synthetic epothilones including but not limited to
- 5 epothilone A, epothilone B, epothilone C, epothilone D, desoxyepothilone A, desoxyepothilone B, [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7-11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17 oxabicyclo
- 10 [14.1.0]heptadecane-5,9-dione (disclosed in US Patent 6,262,094, issued July 17, 2001), [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4-17-
- 15 dioxabicyclo[14.1.0]- heptadecane-5,9-dione (disclosed in USSN 09/506,481 filed on February 17, 2000, and examples 7 and 8 herein), and derivatives thereof; and other microtubule-disruptor agents. Additional antineoplastic agents include, discodermolide (see Service, (1996)
- 20 Science, 274:2009) estramustine, nocodazole, MAP4, and the like. Examples of such agents are also described in the scientific and patent literature, see, e.g., Bulinski (1997) *J. Cell Sci.* 110:3055 3064; Panda (1997) *Proc. Natl. Acad. Sci. USA* 94:10560-10564; Muhlradt (1997)
- 25 Cancer Res. 57:3344-3346; Nicolaou (1997) *Nature* 387:268-272; Vasquez (1997) *Mol. Biol. Cell.* 8:973-985; Panda (1996) *J. Biol. Chem* 271:29807-29812.

In cases where it is desirable to render aberrantly proliferative cells quiescent in conjunction with or

30 prior to treatment with the chemotherapeutic methods of the invention, hormones and steroids (including synthetic analogs): 17a-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate,

35 Methylprednisolone, Methyl-testosterone, Prednisolone,



Triamcinolone, hlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, Zoladex can also be administered to the  
5 patient.

Also suitable for use in the combination chemotherapeutic methods of the invention are antiangiogenics such as matrix metalloproteinase inhibitors, and other VEGF inhibitors, such as anti-VEGF  
10 antibodies and small molecules such as ZD6474 and SU6668 are also included. Anti- Her2 antibodies from Genetech may also be utilized. A suitable EGFR inhibitor is EKB-569 (an irreversible inhibitor). Also included are Imclone antibody C225 immunospecific for the EGFR, and  
15 src inhibitors.

Also suitable for use as an antiproliferative cytostatic agent is Casodex<sup>TM</sup> which renders androgen-dependent carcinomas non-proliferative. Yet another example of a cytostatic agent is the antiestrogen  
20 Tamoxifen which inhibits the proliferation or growth of estrogen dependent breast cancer. Inhibitors of the transduction of cellular proliferative signals are cytostatic agents. Examples are epidermal growth factor inhibitors, Her-2 inhibitors, MEK-1 kinase inhibitors,  
25 MAPK kinase inhibitors, PI3 inhibitors, Src kinase inhibitors, and PDGF inhibitors.

As mentioned, certain anti-proliferative agents are anti-angiogenic and antivascular agents and, by interrupting blood flow to solid tumors, render cancer  
30 cells quiescent by depriving them of nutrition. Castration, which also renders androgen dependent carcinomas non-proliferative, may also be utilized. Starvation by means other than surgical disruption of blood flow is another example of a cytostatic agent. A  
35 particularly preferred class of antivascular cytostatic

agents is the combretastatins. Other exemplary  
cytostatic agents include MET kinase inhibitors, MAP  
kinase inhibitors, inhibitors of non-receptor and  
receptor tyrosine kinases, inhibitors of integrin  
5 signaling, and inhibitors of insulin-like growth factor  
receptors.

Thus, the present invention provides methods for the  
synergistic treatment of a variety of cancers, including,  
but not limited to, the following:

10 carcinoma including that of the bladder  
(including accelerated and metastatic bladder cancer),  
breast, colon (including colorectal cancer), kidney,  
liver, lung (including small and non-small cell lung  
cancer and lung adenocarcinoma), ovary, prostate, testes,  
15 genitourinary tract, lymphatic system, rectum, larynx,  
pancreas (including exocrine pancreatic carcinoma),  
esophagus, stomach, gall bladder, cervix, thyroid, and  
skin (including squamous cell carcinoma);

hematopoietic tumors of lymphoid lineage  
20 including leukemia, acute lymphocytic leukemia, acute  
lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma,  
Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell  
lymphoma, histiocytic lymphoma, and Burketts lymphoma;

hematopoietic tumors of myeloid lineage  
25 including acute and chronic myelogenous leukemias,  
myelodysplastic syndrome, myeloid leukemia, and  
promyelocytic leukemia;

tumors of the central and peripheral nervous  
system including astrocytoma, neuroblastoma, glioma, and  
30 schwannomas;

tumors of mesenchymal origin including  
fibrosarcoma, rhabdomyosarcoma, and osteosarcoma; and  
other tumors including melanoma, xenoderma  
pigmentosum, keratoactanthoma, seminoma, thyroid  
35 follicular cancer, and teratocarcinoma.

Most preferably, the invention is used to treat accelerated or metastatic cancers of the bladder, pancreatic cancer, prostate cancer, non-small cell lung cancer, colorectal cancer, and breast cancer.

5 In a preferred embodiment of this invention, a method is provided for the synergistic treatment of cancerous tumors. Advantageously, the synergistic method of this invention reduces the development of tumors, reduces tumor burden, or produces tumor regression in a  
10 mammalian host.

Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature.

15 For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR), e.g., 1996 edition (Medical Economics Company, Montvale, NJ 07645-1742, USA); the disclosure of which is incorporated herein by reference  
20 thereto.

Preferred compounds of Formula I for use in the methods of the present invention include: [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione; [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione; [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,10-dioxo-13-cyclohexadecene-2,6-dione; [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-  
30 5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-

- thiazolyl)ethenyl]-1,10-dioxa-13-cyclohexadecene-2,6-dione; [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,14,17-
- 5 trioxabicyclo[14.1.0]heptadecane-5,9-dione; [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,14,17-
- 10 trioxabicyclo[14.1.0]heptadecane-5,9-dione; [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione; [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione; [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-
- 15 dioxabicyclo[14.1.0]heptadecane-9-one; [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one; [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-3,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-
- 20 dioxabicyclo[14.1.0]heptadecane-5,9-dione; [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-3,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione; [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13,16-hexamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione; [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,16-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;
- 30
- 35

- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione; [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-6,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione; [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione; [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione; [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione; [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione; [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-4,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione; [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-4,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione; [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-1,5,5,7,9,13-hexamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione; [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-1,5,5,7,9-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-13-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione; [1S-
- 5 [1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-13-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione; [4S-
- 10 [4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-dione; [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-
- 15 5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-dione; [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-14-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-
- 20 8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-14-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione; [4S-
- [4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-
- 25 thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione; [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione; [1S-[1R\*,3R\*,7R\*,10S\*,11R\*,12R\*,16S\*]]-N-phenyl-
- 30 7,11-dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide; [1S-[1R\*,3R\*,7R\*,10S\*,11R\*,12R\*,16S\*]]-N-phenyl-7,11-dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;
- 35 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*]]-N-phenyl-4,8-dihydroxy-

5,5,7,9,13-pentamethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;  
 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*]]-N-phenyl-4,8-dihydroxy-  
 5,5,7,9-tetramethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-  
 5 16-carboxamide; [1S[1R\*,3R\*(E),7R\*,10S\*,  
 11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-  
 3-[1-methyl-2-(2-methyl-4-thiazolyl)cyclopropyl]-4,17-  
 dioxabicyclo[14.1.0]heptadecane-5,9-dione; [1S-  
 [1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
 10 8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-  
 thiazolyl)cyclopropyl]-4,17-  
 dioxabicyclo[14.1.0]heptadecane-5,9-dione; and [4S-  
 [4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-  
 pentamethyl-16-[1-methyl-2-(2-hydroxymethyl-4-  
 15 thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione;  
 and pharmaceutically acceptable salts, solvates and  
 hydrates thereof.

Preferred compounds of Formula II for use in the  
 methods of the invention include:

20 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-  
 (Azidomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-  
 dihydroxy-8,8,10,12,16-pentamethyl-4,17-  
 dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
 25 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-  
 (Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-  
 dihydroxy-8,8,10,12,16-pentamethyl-4,17-  
 dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
 30 [[[1,1-Dimethylethoxy)carbonyl]amino]methyl]-4-  
 thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-  
 pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-  
 dione;  
 35 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-16-[2-[2-[[[(1,1-  
 Dimethylethoxy)carbonyl]amino]methyl]-4-thiazolyl]-1-

- methyl-ethenyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-1-oxa-13(Z)-cyclohexadecene-2,6-dione;  
[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-16-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-4,8-dihydroxy-5,5,7,9,13-
- 5 pentamethyl-1-oxa-13(Z)-cyclohexadecene-2,6-dione;  
[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(pentanoyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 10 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(naphthoyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-
- 15 3-[2-[2-[(2-methoxyethoxy)acetyloxy)methyl]-1-methyl-4-thiazolyl]ethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(N-
- 20 propionylamino)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(3-Acetyl-2,3-dihydro-2-methylene-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-
- 25 dioxabicyclo[14.1.0]heptadecane-5,9-dione, N-oxide;  
[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-3-[2-[2-(methoxymethyl)-4-thiazolyl]-1-methylethenyl]-8,8,10,12-tetramethyl-4,17-
- dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 30 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-(phenoxymethyl)-4-thiazolyl]ethenyl]-4,17-
- dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-
- 35 [(Ethylthio)methyl]-4-thiazolyl]-1-methylethenyl]-7,11-



- dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Ethoxymethyl)-4-thiazolyl]-1-methylethenyl]-7,11-
- 5 dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(2,3,4,6-tetraacetyl-alpha-glucosyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(2',3',4',6'-tetraacetyl-beta-glucosyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(6'-acetyl-alpha-glucosyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-
- 15 dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(p-toluenesulfonyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 20 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Bromomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(5-Bromo-2-methyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Cyanomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-
- 30 dihydroxy-8,8,10,12,16-pentamethyl-4,17-
- 35

- dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-16-[2-[2-(Cyanomethyl)-4-thiazolyl]-1-methylethenyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-1-oxa-13(Z)-cyclohexadecene-2,6-dione;
- 5 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-3-[2-[2-(1H-imidazol-1-ylmethyl)-4-thiazolyl]-1-methylethenyl]-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 10 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Formyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Formyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-
- 15 8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Ethenyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-
- 20 8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-3-[2-[2-(methoxyimino)-4-thiazolyl]-1-methylethenyl]-8,8,10,12-tetramethyl-4,17-
- 25 dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[[ (phenylmethyl)imino]methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 30 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Acetyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-
- 35 8,8,10,12-tetramethyl-3-[1-methyl-2-(2-oxiranyl-4-

- thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-3-[2-[2-(2-iodoethenyl)-4-thiazolyl]-1-methylethenyl]-
- 5 8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Ethynyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-
- 10 8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(methylamino)methyl]-4-thiazolyl]ethenyl]-4,17-
- 15 dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-[[2-(Dimethylamino)ethyl]amino]methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 20 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-[(Dimethylamino)methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-[[Bis(2-methoxyethyl)amino]methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 25 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(4-methyl-1-piperazinyl)methyl]-4-thiazolyl]ethenyl]-4,17-
- 30 dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-4-[2-(7,11-Dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecan-3-yl)-1-propenyl]-2-
- 35 thiazolecarboxylic acid;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-4-[2-(7,11-Dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecan-3-yl)-1-propenyl]-2-thiazolecarboxylic acid methyl ester

5 and the pharmaceutically acceptable salts, solvents and hydrates thereof.

The Formula I compounds may be prepared by the procedures described in WO/9902514. The Formula II compounds may be prepared by the procedures described in  
10 US Patent 6,262,094.

The compounds of Formulas I and II are useful in various pharmaceutically acceptable salt forms. The term "pharmaceutically acceptable salt" refers to those salt forms which would be apparent to the pharmaceutical  
15 chemist, i.e., those which are substantially non-toxic and which provide the desired pharmacokinetic properties, palatability, absorption, distribution, metabolism or excretion. Other factors, more practical in nature, which are also important in the selection, are cost of  
20 the raw materials, ease of crystallization, yield, stability, hygroscopicity and flowability of the resulting bulk drug. Conveniently, pharmaceutical compositions may be prepared from the active ingredients or their pharmaceutically acceptable salts in combination  
25 with pharmaceutically acceptable carriers.

Pharmaceutically acceptable salts of the Formula I and II compounds which are suitable for use in the methods and compositions of the present invention include, but are not limited to, salts formed with a  
30 variety of organic and inorganic acids such as hydrogen chloride, hydroxymethane sulfonic acid, hydrogen bromide, methanesulfonic acid, sulfuric acid, acetic acid, trifluoroacetic acid, maleic acid, benzenesulfonic acid, toluenesulfonic acid, sulfamic acid, glycolic acid,  
35 stearic acid, lactic acid, malic acid, pamoic acid,

sulfanilic acid, 2-acetoxybenzoic acid, fumaric acid, toluenesulfonic acid, methanesulfonic acid, ethanedisulfonic acid, oxalic acid, isethonic acid, and include various other pharmaceutically acceptable salts, such as, e.g., nitrates, phosphates, borates, tartrates, citrates, succinates, benzoates, ascorbates, salicylates, and the like. Cations such as quaternary ammonium ions are contemplated as pharmaceutically acceptable counterions for anionic moieties.

Preferred salts of Formula I and II compounds include hydrochloride salts, methanesulfonic acid salts and trifluoroacetic acid salts. In addition, pharmaceutically acceptable salts of the Formula I and/or II compounds may be formed with alkali metals such as sodium, potassium and lithium; alkaline earth metals such as calcium and magnesium; organic bases such as dicyclohexylamine, tributylamine, and pyridine; and amino acids such as arginine, lysine and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base, in a suitable solvent or solvent combination.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the combinations of this invention, with or without pharmaceutically acceptable carriers or diluents. The synergistic pharmaceutical compositions of this invention comprise an anti-proliferative agent or agents, a formula I compound, and a pharmaceutically acceptable carrier. The methods entail the use of a neoplastic agent in combination with

a Formula I and/or Formula II compound. The compositions of the present invention may further comprise one or more pharmaceutically acceptable additional ingredient(s) such as alum, stabilizers, antimicrobial agents, buffers, coloring agents, flavoring agents, adjuvants, and the like. The antineoplastic agents, Formula I, Formula II compounds and compositions of the present invention may be administered orally or parenterally including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use, the antineoplastic agents, Formula I and/or Formula II compounds and compositions of this invention may be administered, for example, in the form of tablets or capsules, powders, dispersible granules, or cachets, or as aqueous solutions or suspensions. In the case of tablets for oral use, carriers which are commonly used include lactose, corn starch, magnesium carbonate, talc, and sugar, and lubricating agents such as magnesium stearate are commonly added. For oral administration in capsule form, useful carriers include lactose, corn starch, magnesium carbonate, talc, and sugar. When aqueous suspensions are used for oral administration, emulsifying and/or suspending agents are commonly added.

In addition, sweetening and/or flavoring agents may be added to the oral compositions. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient(s) are usually employed, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of the solute(s) should be controlled in order to render the preparation isotonic.

For preparing suppositories according to the invention, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the

active ingredient is dispersed homogeneously in the wax, for example by stirring. The molten homogeneous mixture is then poured into conveniently sized molds and allowed to cool and thereby solidify.

5        Liquid preparations include solutions, suspensions and emulsions. Such preparations are exemplified by water or water/propylene glycol solutions for parenteral injection. Liquid preparations may also include solutions for intranasal administration.

10        Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid preparations which are  
15        intended for conversion, shortly before use, to liquid preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of Formula I and II, as well as the  
20        anti-neoplastic agents, described herein may also be delivered transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the  
25        art for this purpose.

The combinations of the present invention may also be used in conjunction with other well known therapies that are selected for their particular usefulness against the condition that is being treated.

30        If formulated as a fixed dose, the active ingredients of the combination compositions of this invention are employed within the dosage ranges described below. Alternatively, the anti-neoplastic, and Formula I and Formula II compounds may be administered separately  
35        in the dosage ranges described below. In a preferred

embodiment of the present invention, the antineoplastic agent is administered in the dosage range described below following or simultaneously with administration of the Formula I compound in the dosage range described below.

5

Table I sets forth preferred chemotherapeutic combinations and exemplary dosages for use in the methods of the present invention. Where "Compound of Formula I" appears, any of the variations of Formula I or Formula II set forth herein are contemplated for use in the chemotherapeutic combinations. Preferably, Compound 1 or Compound 4 is employed.

TABLE 1

15	<b>CHEMOTHERAPEUTIC COMBINATION</b>	<b>DOSAGE mg/m<sup>2</sup> (per dose)</b>
	Compound of Formula I + Cisplatin	0.1-100 mg/m <sup>2</sup> 5-150 mg/m <sup>2</sup>
20	Compound of Formula I + Carboplatin	0.1-100 mg/m <sup>2</sup> 5-1000 mg/m <sup>2</sup>
	Compound of Formula I + Radiation	0.1-100 mg/m <sup>2</sup> 200-8000 cGy
25	Compound of Formula I + CPT-11	0.1-100 mg/m <sup>2</sup> 5-400 mg/m <sup>2</sup>
	Compound of Formula I + Paclitaxel	0.1-100 mg/m <sup>2</sup> 40-250 mg/m <sup>2</sup>
30	Compound of Formula I + Paclitaxel + Carboplatin	0.1-100 mg/m <sup>2</sup> 40-250 mg/m <sup>2</sup> 5-1000 mg/m <sup>2</sup>
35	Compound of Formula I + 5FU and optionally + Leucovorin	0.1-100 mg/m <sup>2</sup> 5-5000 mg/m <sup>2</sup> 5-1000 mg/m <sup>2</sup>
40	Compound of Formula I + Etoposide	0.1-100 mg/m <sup>2</sup> 1-500 mg/m <sup>2</sup>
	Compound of Formula I + Gemcitabine	0.1-100 mg/m <sup>2</sup> 100-3000 mg/m <sup>2</sup>

45



	Compound of Formula I + UFT and optionally + leucovorin	0.1-100 mg/m2 50-800 mg/m2 5-1000 mg/m2
5	Compound of Formula I + Gemcitabine + Cisplatin	0.1-100 mg/m2 100-3000 mg/m2 5-150 mg/m2
10	Compound of Formula I +UFT +Leucovorin	0.1-100 mg/m2 50-800 mg/m2 5-1000 mg/m2
15	Compound of Formula I + Cisplatin + paclitaxel	0.1-100 mg/m2 5-150 mg/m2 40-250 mg/m2
20	Compound of Formula I + Cisplatin + 5FU	0.1-100 mg/m2 5-150 mg/m2 5-5000 mg/m2
25	Compound of Formula I + Oxaliplatin + CPT-11	0.1-100 mg/m2 5-200 mg/m2 4-400 mg/m2
30	Compound of Formula I + 5FU + CPT-11 and optionally + leucovorin	0.1-100 mg/m2 5-5000 mg/m2 4-400 mg/m2 5-1000 mg/m2
35	Compound of Formula I + radiation + 5FU + Cisplatin	0.1-100 mg/m2 200-8000 cGy 5-5000 mg/m2 5-150 mg/m2
40	Compound of Formula I + Oxaliplatin + 5FU and optionally + Leucovorin	0.1-100 mg/m2 5-200 mg/m2 5-5000 mg/m2 5-1000 mg/m2
45	Compound of Formula I + paclitaxel + CPT-11	0.1-100 mg/m2 40-250 mg/m2 4-400 mg/m2
50	Compound of Formula I + paclitaxel + 5-FU	0.1-100 mg/m2 40-250 mg/m2 5-5000 mg/m2

	Compound of Formula I	0.1-100 mg/m <sup>2</sup>
	+ UFT	50-800 mg/m <sup>2</sup>
	+ CPT-11 and optionally	4-400 mg/m <sup>2</sup>
5	+ leucovorin	5-1000 mg/m <sup>2</sup>

In the above Table I, "5FU" denotes 5-fluorouracil, "Leucovorin" can be employed as leucovorin calcium, "UFT" is a 1:4 molar ratio of tegafur:uracil, and "Epothilone" is preferably a compound described in WO 99/02514 or WO 00/50423, both incorporated by reference herein in their entirety.

While Table I provides exemplary dosage ranges of the Formula I and Formula II compounds and certain anticancer agents of the invention, when formulating the pharmaceutical compositions of the invention the clinician may utilize preferred dosages as warranted by the condition of the patient being treated. For example, Compound 1 may preferably administered at 25-60 mg/m<sup>2</sup> every 3 weeks. Compound 2, may preferably be administered at a dosage ranging from 25-500 mg/m<sup>2</sup> every three weeks for as long as treatment is required. Preferred dosages for cisplatin are 75-120 mg/m<sup>2</sup> administered every three weeks. Preferred dosages for carboplatin are within the range of 200-600 mg/m<sup>2</sup> or an AUC of 0.5-8 mg/ml x min; most preferred is an AUC of 4-6 mg/ml x min. When the method employed utilizes radiation, preferred dosages are within the range of 200-6000 cGY. Preferred dosages for CPT-11 are within 100-125 mg/m<sup>2</sup>, once a week. Preferred dosages for paclitaxel are 130-225 mg/m<sup>2</sup> every 21 days. Preferred dosages for gemcitabine are within the range of 80-1500 mg/m<sup>2</sup> administered weekly. Preferably UFT is used within a range of 300-400 mg/m<sup>2</sup> per day when combined with leucovorin administration. Preferred dosages for leucovorin are 10-600 mg/m<sup>2</sup> administered weekly.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small amounts until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired. Intermittent therapy (e.g., one week out of three weeks or three out of four weeks) may also be used.

Certain cancers can be treated effectively with compounds of Formula I and/or Formula II and a plurality of anticancer agents. Such triple and quadruple combinations can provide greater efficacy. When used in such triple and quadruple combinations the dosages set forth above can be utilized. Other such combinations in the above Table I can therefore include "Compound 1" in combination with (1) mitoxantrone + prednisone; (2) doxorubicin + carboplatin; or (3) herceptin + tamoxifen.

5-FU can be replaced by UFT in any of the above combinations.

When employing the methods or compositions of the present invention, other agents used in the modulation of tumor growth or metastasis in a clinical setting, such as antiemetics, can also be administered as desired.

The present invention encompasses a method for the synergistic treatment of cancer wherein a neoplastic agent and a Formula I and/or Formula II compound are administered simultaneously or sequentially. Thus, while a pharmaceutical formulation comprising antineoplastic agent(s) and a Formula I and/or Formula II compound may be advantageous for administering the combination for one particular treatment, prior administration of the anti-

neoplastic agent(s) may be advantageous in another treatment. It is also understood that the instant combination of antineoplastic agent(s) and Formula I and/or Formula II compound may be used in conjunction  
5 with other methods of treating cancer (preferably cancerous tumors) including, but not limited to, radiation therapy and surgery. It is further understood that a cytostatic or quiescent agent, if any, may be administered sequentially or simultaneously with any or  
10 all of the other synergistic therapies.

The combinations of the instant invention may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. Combinations  
15 of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a multiple combination formulation is inappropriate.

The chemotherapeutic agent(s) and/or radiation  
20 therapy can be administered according to therapeutic protocols well known in the art. It will be apparent to those skilled in the art that the administration of the chemotherapeutic agent(s) and/or radiation therapy can be varied depending on the disease being treated and the  
25 known effects of the chemotherapeutic agent(s) and/or radiation therapy on that disease. Also, in accordance with the knowledge of the skilled clinician, the therapeutic protocols (e.g., dosage amounts and times of administration) can be varied in view of the observed  
30 effects of the administered therapeutic agents (i.e., antineoplastic agent(s) or radiation) on the patient, and in view of the observed responses of the disease to the administered therapeutic agents.

In the methods of this invention, a compound of  
35 Formula I or Formula II is administered simultaneously or

sequentially with an anti-proliferative agent and/or radiation. Thus, it is not necessary that the chemotherapeutic agent(s) and compound of Formula I and/or Formula II, or the radiation and the compound of  
5 Formula I and/or Formula II, be administered simultaneously or essentially simultaneously. The advantage of a simultaneous or essentially simultaneous administration is well within the determination of the skilled clinician.

10 Also, in general, the compound of Formula I and/or Formula II, and chemotherapeutic agent(s) do not have to be administered in the same pharmaceutical composition, and may, because of different physical and chemical  
15 characteristics, have to be administered by different routes. For example, the compound of Formula I or II may be administered orally to generate and maintain good blood levels thereof, while the chemotherapeutic agent(s) may be administered intravenously. The determination of  
20 the mode of administration and the advisability of administration, where possible, in the same pharmaceutical composition, is well within the knowledge of the skilled clinician. The initial administration can be made according to established protocols known in the  
25 art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

The particular choice of compound of Formula I and/or II and anti-proliferative cytotoxic agent(s) or radiation will depend upon the diagnosis of the attending  
30 physicians and their judgment of the condition of the patient and the appropriate treatment protocol.

If the compound of Formula I and/or Formula II and the anti-neoplastic agent(s) and/or radiation are not administered simultaneously or essentially  
35 simultaneously, then the initial order of administration

of the compound of Formula I and/or Formula II, and the chemotherapeutic agent(s) and/or radiation, may be varied. Thus, for example, the compound of Formula I and/or II may be administered first followed by the administration of the antiproliferative agent(s) and/or radiation; or the antiproliferative agent(s) and/or radiation may be administered first followed by the administration of the compound of Formula I and/or Formula II. This alternate administration may be repeated during a single treatment protocol. The determination of the order of administration, and the number of repetitions of administration of each therapeutic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the disease being treated and the condition of the patient. For example, the anti-neoplastic agent(s) and/or radiation may be administered initially, especially if a cytotoxic agent is employed. The treatment is then continued with the administration of the compound of Formula I and/or II and optionally followed by administration of a cytostatic agent, if desired, until the treatment protocol is complete.

Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of a component (therapeutic agent--i.e., compound of Formula I and/or II, anti-neoplastic agent(s), or radiation) of the treatment according to the individual patient's needs, as the treatment proceeds.

The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the patient as well as more definite signs such as relief of disease-related symptoms, inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as

radiological studies, e.g., CAT or MRI scan, and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

In order to facilitate a further understanding of the invention, the following examples are presented primarily for the purpose of illustrating more specific details thereof. The scope of the invention should not be deemed limited by the examples, but to encompass the entire subject matter defined by the claims.

15

#### **Experimental protocol**

##### **Compounds:**

The following designations are used to identify the test compounds throughout the examples:

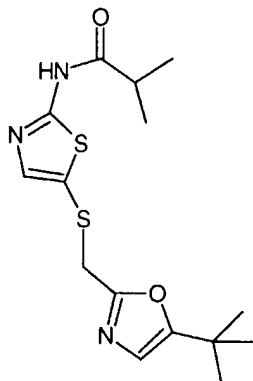
20

**Compound 1:** [1S-1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione

25

**Compound 2:** (R)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(2-thienylsulfonyl)-1H-1,4-benzodiazepine-7-carbonitrile, hydrochloride salt

**Compound 3:** A CDK inhibitor is shown below



5

**Compound 4:** 1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.

**Compound 5:** N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide.

15

#### Chemicals and solutions:

Unless specified, chemicals and solutions used for the maintenance of cell culture were obtained from GIBCO/BRL.  
Sterile tissue culture ware was obtained from Corning, NY.  
All other reagents were from Sigma or Fisher at the highest grade available.

20

#### Drug Administration:

For administration of Compound 1 (an epothilone) to rodents, two different excipients have been used: (1)

25



ethanol/water (1:9, v/v) and (2) Cremophor®/  
ethanol/water (1:1:8, v/v). Compound 1 was first  
dissolved in ethanol or a mixture of Cremophor®/ethanol  
(50:50). Final dilution to the required dosage strength  
5 is made less than 1 h before drug administration. For  
parenteral administration (IV), dilution was made with  
water so that the dosing solutions contain the specified  
excipient composition described above. For oral  
administration (PO), the dilution was made with 0.25 M  
10 sodium phosphate buffer (pH=8.0) at a ratio of 30/70,  
v/v. Paclitaxel was dissolved in a 50/50 mixture of  
ethanol and Cremophor® and stored at 4°C; final dilution  
of paclitaxel was obtained immediately before drug  
administration with NaCl 0.9%. The volume of all  
15 compounds injected was 0.01 ml/g of mice, and 0.005 ml/g  
of rats.

#### Tumor cell lines:

HCT116 human carcinoma cell lines and HCT116/VM46  
20 cells, a MDR variant [1], were maintained in McCoy's 5A  
medium (GIBCO) and 10% heat inactivated fetal bovine serum  
(GIBCO). A2780 human ovarian carcinoma cells and A2780Tax  
cells obtained from Dr. Antonio Fojo (NCI, Bethesda, MD)  
were maintained in IMEM (GIBCO) and 10% fetal bovine serum  
25 (GIBCO). This paclitaxel resistant cell line does not  
overexpress P-glycoprotein but has point mutations in the  
M40 isotype of beta-tubulin [2]. Purified tubulin isolated  
from these resistant cells is refractory to polymerization  
by paclitaxel and is thought to account for the resistance  
30 to this drug, and collateral sensitivity to microtubule  
depolymerizing agents, such as vinblastine.

#### Cytotoxicity assay:

The *in vitro* cytotoxicity was assessed in tumor  
35 cells by a tetrazolium-based colorimetric assay which  
takes advantage of the metabolic conversion of MTS (3-

(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphenyl)-2H-tetrazolium, inner salt) to a reduced form that absorbs light at 492 nm [3]. Cells were seeded 24 hr prior to drug addition. Following a 72 hour  
5 incubation at 37°C with serially diluted compound, MTS, in combination with the electron coupling agent phenazine methosulfate, was added to the cells. The incubation was continued for 3 hours, then the absorbancy of the medium at 492 nm was measured with a spectrophotometer to obtain  
10 the number of surviving cells relative to control populations. The results are expressed as median cytotoxic concentrations (IC50 values).

Clonogenic cell colony-formation assay:

15 The potency with which Compound 1 and paclitaxel kill clonogenic tumor cells (cells that are able to divide indefinitely to form a colony) *in vitro* was evaluated by a colony formation assay. The concentration needed to kill clonogenic HCT-116 human colon carcinoma  
20 cells by 90% (i.e., the IC<sub>90</sub>) was determined. Analysis of the effects of combination treatment *in vitro* was by the isobologram and multiplicity methods described by Stephens and Steel [4]

25 Tubulin polymerization assay:

The potency with which Compound 1 and paclitaxel polymerize tubulin isolated from calf brain was evaluated by published technique [5, 6].

30 Animals:

All rodents were obtained from Harlan Sprague Dawley Co. (Indianapolis, Indiana), and maintained in an ammonia-free environment in a defined and pathogen-free colony. The animal care program of Bristol-Myers Squibb  
35 Pharmaceutical Research Institute is fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC).

In Vivo Antitumor Testing:

The following human tumors were used: A2780 ovarian, A2780Tax ovarian (established from cells obtained from Dr. Antonio Fojo, Medicine Branch, NCI, Bethesda, MD), HCT116/VM46 colon, Pat-7 ovarian (established from a tumor biopsy provided by Dr. Thomas Hamilton, Fox Chase Cancer Center, Philadelphia, PA) from a patient who had developed resistance to TAXOL<sup>®</sup>). The murine fibrosarcoma M5076 was also employed.

The human tumors were maintained in Balb/c nu/nu nude mice. M5076 was maintained in C57BL/6 mice. Tumors were propagated as subcutaneous transplants in the appropriate mouse strain using tumor fragments obtained from donor mice.

The following tumors were passaged in the indicated host strain of mouse: murine M5076 fibrosarcoma (M5076) in C57Bl/6 mice; human A2780 and Pat-7 ovarian carcinomas, HCT116, HCT116/VM46 and LS174T colon carcinoma, Pat-21 breast carcinoma in nude mice. Tumor passage occurred biweekly for murine tumors and approximately every two to eight weeks for the various human tumor lines. With regard to efficacy testing, M5076 tumors were implanted in (C57Bl/6 x DBA/2)F1 hybrid mice, and human tumors were implanted in nude mice. All tumor implants for efficacy testing were subcutaneous (sc).

The required number of animals needed to detect a meaningful response were pooled at the start of the experiment and each was given a subcutaneous implant of a tumor fragment (• 50 mg) with a 13-gauge trocar. For treatment of early-stage tumors, the animals were again pooled before distribution to the various treatment and control groups. For treatment of animals with advanced-stage disease, tumors were allowed to grow to the pre-determined size window (tumors outside the range were excluded) and animals were evenly distributed to various

treatment and control groups. Treatment of each animal was based on individual body weight. Treated animals were checked daily for treatment related toxicity/mortality. Each group of animals was weighed before the initiation  
5 of treatment (Wt1) and then again following the last treatment dose (Wt2). The difference in body weight (Wt2-Wt1) provides a measure of treatment-related toxicity.

Tumor response was determined by measurement of tumors with a caliper twice a week, until the tumors  
10 reach a predetermined "target" size of 1 gm. Tumor weights (mg) were estimated from the formula:

$$\text{Tumor weight} = (\text{length} \times \text{width}^2) \div 2$$

15

Antitumor activity was evaluated at the maximum tolerated dose (MTD) which is defined as the dose level immediately below which excessive toxicity (i.e. more than one death) occurred. The MTD was frequently  
20 equivalent to OD. When death occurs, the day of death was recorded. Treated mice dying prior to having their tumors reach target size were considered to have died from drug toxicity. No control mice died bearing tumors less than target size. Treatment groups with more than one death  
25 caused by drug toxicity were considered to have had excessively toxic treatments and their data were not included in the evaluation of a compound's antitumor efficacy.

Tumor response end-point was expressed in terms of  
30 tumor growth delay (T-C value), defined as the difference in time (days) required for the treated tumors (T) to reach a predetermined target size compared to those of the control group (C).

To estimate tumor cell kill, the tumor volume doubling time was first calculated with the formula:

TVDT = Median time (days) for control tumors to reach  
5 target size - Median time (days) for control tumors to  
reach half the target size

And,  $\text{Log cell kill} = T - C \div (3.32 \times \text{TVDT})$

10 Statistical evaluations of data were performed using  
Gehan's generalized Wilcoxon test [7].

EXAMPLE ICOMPOUND 1 DEMONSTRATES CYTOTOXICITY AGAINSTCANCER CELLS IN VITRO

5  
Compound 1 has a broad spectrum of activity against  
a panel of tumor cell lines *in vitro*. Of the 21 cells  
lines tested (Figure 1), 18 have IC<sub>50</sub> values between 1.4-  
6 nM. Three cell lines have IC<sub>50</sub> values greater than 6  
10 nM: viz. two highly multi-drug resistant (MDR) colon  
tumor lines HCT116/VM46 (24.5 nM) and MIP (24.8 nM), and  
the normal mouse lung fibroblast cell line MLF (34.5 nM).  
It should be noted that Compound 1 did substantially  
"overcome" the multidrug resistance inherent in these  
15 cell lines. Thus, for paclitaxel, the ratios of  
concentrations (R/S, or resistance ratio) required to  
inhibit cell growth by 50% in these resistant lines  
versus those required for the sensitive HCT116 line were  
155 and >>55 respectively, for HCT116/VM46 and MIP. In  
20 comparison, the R/S ratios for Compound 1 were only 9.4  
and 9.5, respectively (Table 2).

**Table 2. *In vitro* Cytotoxicity of Compound 1 and Paclitaxel in Paclitaxel-Sensitive and -Resistant Tumor Cell Lines.**

Compound	<u>IC<sub>50</sub>, nM (resistance ratio)</u>		
	HCT-116	HCT116/VM46	MIP
Paclitaxel	2.1	326 (155)	>>112 (>>53)
Compound 1	2.6	24.5 (9.4)	24.8 (9.5)

### 5 Mechanism of Cytotoxicity - Tubulin Polymerization

The cytotoxic activities of the epothilones, like those of the taxanes, have been linked to stabilization of microtubules which results in mitotic arrest at the G2/M transition. In this regard the potency of Compound 1 is similar to those of its two natural analogs, epothilones A and B (Table 3).

**Table 3. Tubulin Polymerization Potency of Three Epothilones Relative to Paclitaxel**

Analogue	Polymerization Potency, EC <sub>0.01</sub> (μM)	Ratio of Polymerization Potency of Analogue/Paclitaxel
Compound 1	3.5	0.4
(Epothilone A)	2.0	0.4
(Epothilone B)	1.8	0.3
Paclitaxel	8.5, 5.0, 6.0	1.0

15

### **EXAMPLE 2** **COMPOUND 1 INHIBITS CELL CYCLE PROGRESSION**

20

Similar to paclitaxel, Compound 1 blocks cells in the mitotic phase of the cell division cycle. Moreover, the concentration of Compound 1 needed to arrest cells in

mitosis corresponds well to the concentration required to kill cells over the same treatment duration. Thus, as shown in Figure 2, Compound 1 at a concentration close to the IC90 value ( $\approx 7.5$  nM) almost completely blocks cells in mitosis in 8 hours.

**EXAMPLE 3**  
**Combination chemotherapy in vitro**

The success of an anticancer agent is dependent not only on its antitumor activity as a single agent but also on its ability to combine successfully with other antineoplastic drugs. Like paclitaxel, Compound 1 induces profound cell cycle perturbation by arresting cells in mitosis. For these reasons, it is particularly pertinent to investigate the behavior of Compound 1 when used in combination chemotherapy. Colony-formation assays were used to examine the cytotoxicity of Compound 1 in combination with several selected anticancer agents of diverse mechanisms of action *in vitro*.

Isobologram analyses showed that the mode of interaction between Compound 1 and other cytotoxic agents *in vitro* is drug-, sequence- and dose-dependent, and can vary from synergism to antagonism (Table 4). For Compound 2, a ras farnesyl transferase inhibitor currently in Phase I clinical study, synergism was observed when Compound 1 was administered first followed by Compound 2 (Figures 3A and 3B). When cells were treated with Compound 1 and Compound 2 simultaneously or in the Compound 2  $\rightarrow$  Compound 1 sequence, only additivity was observed. With Compound 3, a CDK inhibitor, synergy was again observed when Compound 1 was administered first, but antagonism was observed for the other two treatment sequences.

For paclitaxel, all three treatment sequences resulted in additivity. In the case of cisplatin, additivity was observed when the two agents were used sequentially, but



synergism was obtained for simultaneous treatment.

**Table 4. The effect of sequence of drug exposure on the cytotoxic interaction between Compound 1 and five other antineoplastic agents in the HCT116 human colon carcinoma cell line**

Combination Sequence	Mode of Interaction
+ Compound 2 (ras FT inhibitor)	
Compound 1 → Compound 2	Synergy
Compound 2 → Compound 1	Additivity
Simultaneous	Additivity
+ Compound 3 (CDK inhibitor)	
Compound 1 → Compound 3	Synergy
Compound 3 → Compound 1	Antagonism
Simultaneous	Antagonism
+ Paclitaxel (microtubule stabilizer)	
Compound 1 → Paclitaxel	Additivity
Paclitaxel → Compound 1	Additivity
Simultaneous	Additivity
+ Cisplatin (DNA damaging)	
Compound 1 → Cisplatin	Additivity
Cisplatin → Compound 1	Additivity
Simultaneous	Synergy

5

#### EXAMPLE 4

##### ANTITUMOR ACTIVITY BY PARENTERAL ADMINISTRATION

10

Compound 1 was evaluated in a panel of eight human and murine tumor models. Five were chosen because of their resistance to paclitaxel (Table 5) and three paclitaxel-sensitive models were included in order to gain a full assessment of the spectrum of antitumor activity of Compound 1.

15

### Paclitaxel-refractory Tumor Models

#### *1. Pat-7 clinically-derived TAXOL®-resistant ovarian carcinoma model.*

5           This tumor model was established from a tumor biopsy of an ovarian cancer patient (Pat-7), who was initially responsive to TAXOL® treatment but ultimately developed resistance to it following nine courses of monotherapy with TAXOL®. Prior to treatment with TAXOL®, Pat-7 also received  
10 numerous other chemotherapeutic agents including carboplatin, cytoxan, VP-16, ifosfamide and altretamine. Tumor biopsy was taken following development of TAXOL® resistance.

          Compound 1 was administered to nude mice bearing  
15 staged tumors using an every 2 days x 5 schedule. At optimal dose, it was highly active eliciting 2.1 and 4.5 LCKs in two separate tests (Table 6 and Figure 4). Concomitantly evaluated IV paclitaxel yielded 0.6 and 1.3 LCKs, respectively, at its optimal dose and schedule.

20           To evaluate the activity of Compound 1 in a second species, Pat-7 was implanted into immunocompromised nude rats and Compound 1 was administered on an IV, every 8 days x 2 schedule (Table 6). At the optimal dose of 3 mg/kg/inj, Compound 1 was highly active, yielding 4 of 6 cures. In  
25 comparison, paclitaxel produced 2.2 LCK at its optimal dose and no cures (n=6).

#### *2. A2780Tax human ovarian carcinoma xenograft (mutated tubulin).*

30           A2780Tax is a paclitaxel-resistant human ovarian carcinoma model. It was derived from the sensitive parent A2780 line by co-incubation of cells with paclitaxel and verapamil, an MDR-reversal agent. Its resistance mechanism  
35 has been shown to be non-MDR related and is attributed to

a mutation in the gene encoding the beta-tubulin protein [2].

Compound 1 administered to mice bearing staged tumors on an every 2 days x 5 schedule yielded 2.5 LCK at its MTD (6.3 mg/kg/inj). In comparison, IV paclitaxel yielded 0.8 LCK at its MTD. Compound 1 is significantly better than paclitaxel in this test (Table 6).

3. *HCT116/VM46 human colon carcinoma xenograft (multi-drug resistant).*

10

HCT116/VM46 is an MDR-resistant colon carcinoma developed from the sensitive HCT116 parent line. *In vivo*, grown in nude mice, HCT116/VM46 has consistently demonstrated high resistance to paclitaxel (Table 5). In 12 consecutive studies paclitaxel, at its MTD, elicited low LCKs that ranged from 0-0.9 (median = 0.35 LCK).

Compound 1 treatment of mice bearing staged HCT116/VM46 tumors using an every 2 days x 5 schedule produced significant antitumor effects. At its optimal dose (4.8-6.3 mg/kg/inj) in 3 separate studies, Compound 1 yielded 3.1, 1.3 and 1.8 LCKs. In contrast, concomitantly tested IV paclitaxel yielded 0.4 and 0.7 LCK, respectively, at its MTD in the first two tests.

25 4. *Pat-21, clinically-derived paclitaxel resistant breast cancer model*

Pat-21 is an early passage paclitaxel-resistant tumor model established from a tumor biopsy of a breast cancer patient with metastatic disease who was given, and failed to respond to, an experimental therapy consisting of 5 cycles of TAXOL® in combination with the multidrug resistance reversal agent dexverapamil. Prior to TAXOL® therapy, the patient also received chemotherapy consisting of adriamycin, cytoxan, methotrexate and 5-FU. Tumor biopsies were obtained after cessation of TAXOL® therapy.

Pat-21 grows at a relative slow rate in nude mice, doubling in volume approximately every 3 weeks. For antitumor efficacy evaluation, two courses of Compound 1 or paclitaxel was administered to mice bearing Pat-21 tumors  
5 staged to approximately 100 mg. The two courses were separated by a 3-week interval. Each course consisted of 3 doses given every 4 days. Paclitaxel was completely inactive against this model yielding 0.3 LCK at its MTD of 36 mg/kg/inj. In contrast, Compound 1 was significantly  
10 active, currently yielding LCK value of >1.5 LCK at its optimal dose of 10 mg/kg/inj.

5. *M5076 murine sarcoma model.*

M5076 is a mouse fibrosarcoma that is inherently  
15 refractory to paclitaxel *in vivo*. Compound 1, tested IV on an every 2 days x 5 schedule versus unstaged sc tumors, was inactive at its MTD of 8.4 mg/kg/inj, yielding 0.5 and 0.7 LCKs, respectively, in two separate experiments (Table 6).

Concomitantly tested IV paclitaxel given by its optimal  
20 schedule was also inactive and yielded 0.1 and 0.5 LCK, respectively.

In a separate study, Compound 1 was administered by a less frequent dosing schedule (*viz.*, every 4 days x 3) and demonstrated improved antitumor activity, yielding 1.0 LCK  
25 at the MTD of 24 mg/kg/inj.

<b>Table 5. Tumor Model Characteristics</b>			
<b>Tumor</b>	<b>Histology</b>	<b>Paclitaxel sensitivity</b>	<b>Resistance Mechanism(s)</b>
<b>Human</b>			
Pat-7	Ovarian	Resistant <sup>1</sup>	MDR, MRP <sup>2</sup>
A2780Tax	Ovarian	Resistant	Tubulin mutation
HCT116/VM46	Colon	Resistant	MDR
Pat-21	Breast	Resistant <sup>1</sup>	Unknown
A2780	Ovarian	Sensitive	-
HCT116	Colon	Sensitive	-
LS174T	Colon	Sensitive	-
<b>Murine</b>			
M5076	Fibrosarcoma	Resistant	Unknown, non-MDR

<sup>1</sup> Clinical resistance to TAXOL

<sup>2</sup> MRP = multidrug resistance related protein

Table 6      Preclinical Antitumor Activity of Compound 1 and Paclitaxel Versus Paclitaxel-Resistant Tumors					
Tumor	Expt. No.	Compound 1			PACLITAXEL
		Rt., schedule	OD <sup>1</sup> (mg/kg)	LCK <sup>2</sup> (cures/to tal)	LCK <sup>2, 3</sup>
Human tumors – in nude mice					
Pat-7	R403	IV, q2dx5	4.8	2.1	0.6
	8	IV, q2dx5	6.3	4.5	1.3
	12	IV, q2dx5	6.3	2.1	
A2780Tax	12	IV, q2dx5	6.3	2.5	0.8
HCTVM46	32	IV, q2dx5	4.8	3.1	0.4
	33	IV, q2dx5	4.8	1.3	0.7
	35	IV, q2dx5	6.3	1.8	ND <sup>4</sup>
	35	IV, q4dx3	16	2.0	ND <sup>4</sup>
	Historical paclitaxel responses in 12 consecutive studies				(0.4, 0.7, 0.4, 0.3, 0.3, 0.0, 0.2, 0.1, 0.9, 0.9, 0.3, 0.3)
Pat-21	R667	IV, q4dx3; 41, 68	10	>1.5 <sup>5</sup>	0.3
Human tumors – in nude rats					
Pat-7	15	IV, q8dx2	3	>5 (4/6)	2.2 (0/6)
Murine tumors					
M5076	159	IV, q2dx5	8.4	0.5	0.1
	162	IV, q2dx5	8.4	0.7	0.5
	172	IV, q4dx3	24	1.0	ND

<sup>1</sup> OD, optimal dose or maximum tolerated dose (MTD).

<sup>2</sup> LCK, gross log cell kill. When 50% or greater of the treated animals are cured, LCK value is calculated based on tumor measurement s of the last available date before cure is declared and represents a minimum estimate (>). In such cases, cured rates are also described.

<sup>3</sup> LCK are for optimal dose (dose ranged from 24-36 mg/kg/inj), or highest dose tested if inactive.

<sup>4</sup> ND, not done.

<sup>5</sup> Study still in progress. Interim analysis based on tumor measurement data on the last available date (6/8/99) indicates tumor growth delay equivalent to at least 1.5 LCK.

**Paclitaxel-sensitive tumor Models**

5

*1. A2780 human ovarian carcinoma model.*

A2780 is a fast-growing human ovarian carcinoma model that is highly sensitive to paclitaxel (Table 6). Nude mice bearing staged tumors were treated with Compound 1 using the "paclitaxel-optimized schedule" of IV administration every 2 days for a total of 5 injections (every 2 days x 5). At the maximum tolerated dose (6.3 mg/kg/inj), Compound 1 was highly active yielding >4.8, 2 and 3.1 LCKs in three separate experiments. Concomitantly tested IV paclitaxel, included in the first two studies, yielded 2 and 3.5 LCKs, respectively at its optimal dose.

A2780 grown in nude rats was also utilized. Compound 1, tested at its MTD (1.2 mg/kg/inj), and administered every 2 days x 5, was inactive as tested (0.3 LCK). Concomitantly tested IV paclitaxel was highly active, yielding 5 of 7 cures in this study. Subsequent studies in mice with the A2780 tumors has demonstrated that less frequent dosing of Compound 1 is better tolerated and yields improved activity (see Table 6). Thus, the lack of activity in nude rats for Compound 1 may be due to the suboptimum treatment schedule employed. For example, in subsequent studies using the paclitaxel-resistant Pat-7 tumors, Compound 1 was shown to possess significant antitumor activity when administered on a less frequent dosing schedule of every 8 days x 2 (Table 6).

*2. HCT116 human colon carcinoma model.*

HCT116 is a human colon carcinoma model that has been shown to be highly sensitive to paclitaxel *in vivo*. Compound 1 administered to nude mice bearing staged (~ 100 mg) HCT116 tumors was highly active, producing >6.3 LCKs and a large number of cures at three different treatment schedules: every 2 days x 5 doses, every 4 days x 3 and every 8 days x 2 (Table 7). However, these activities though impressive were comparable to but not superior than the historical results obtained for paclitaxel given at its optimal dose and schedule.

### 3. *LS174T*.

LS174T is a human colon carcinoma model known to be sensitive to paclitaxel. Compound 1, administered every 4 days x 3 produced 2.3 LCKs at its MTD of 16 mg/kg/inj. In comparison, concomitantly tested *iv* paclitaxel yielded 2.0 LCK at its optimal regimen of 36 mg/kg/inj, administered every 2 days for 5 doses (Table 7).



**Table 7. Preclinical Antitumor Activity of Compound 1 and Paclitaxel Versus Paclitaxel-Sensitive Tumors**

Table 7. Preclinical Antitumor Activity of Compound 1 and Paclitaxel Versus Paclitaxel-Sensitive Tumors					
Tumor	Expt. No.	Rt., schedule	Compound 1		Paclitaxel
			OD <sup>1</sup> (mg/kg)	LCK <sup>2</sup> (Cures/total)	LCK <sup>2, 3</sup>
<b>Human tumors – in nude mice</b>					
A2780	89	IV, q2dx5	6.3	>4.8 (3/7)	2
	92	IV, q2dx5	6.3	2	3.5
	111	IV, q2dx5	4.8	3.1	ND <sup>4</sup>
	115	IV, q2dx5	6.3	2.4	ND
	115	IV, q4dx3	16	>5.3	ND
HCT116	52	IV, q2dx5	6.3	>6.3 (4/8)	ND
	52	IV, q4dx3	10	>6.3 (5/8)	ND
	52	IV, q8dx2	24	>6.3 (8/8)	ND
LS174T	R578	IV, q4dx3	16	2.3	2.0
<sup>1</sup> OD, optimal dose or maximum tolerated dose (MTD). <sup>2</sup> LCK, gross log cell kill. When 50% or greater of the treated animals are cured, LCK value is calculated based on tumor measurements of the last date prior to cure is declared and represents a minimum estimate of LCK (>). In such cases, cured rates are also described. <sup>3</sup> LCK are for optimal dose (dose ranged from 24-36 mg/kg), or highest dose tested if inactive. <sup>4</sup> ND, not done.					

5

**EXAMPLE 5****Antitumor Activity by the Oral Route of Administration**

The fact that Compound 1 is significantly more stable at neutral pH than at low pH provided the impetus for the

evaluation of Compound 1 by oral administration (PO) in a pH buffering vehicle (0.25M potassium phosphate, pH 8.0).

Using an every 2 days x 5 schedule, Compound 1 was highly active orally against the Pat-7 human ovarian carcinoma model (Table 8). In two separate experiments oral Compound 1 yielded 3.1 and 2.5 LCKs at its MTD (Figure 5 and Table 8). In comparison, concomitantly tested IV paclitaxel produced 1.3 and 1.2 LCK, respectively at its optimal dose and schedule.

In the HCT116 human colon carcinoma model, orally administered Compound 1 cured seven of eight mice when administered at a dose of 90 mg/kg/adm, every 2 days for 5 doses. Note that this degree of antitumor activity was equivalent to that achieved by the best concomitantly tested IV regimen (every 8 days x 2, see Table 6).

**Table 8. Antitumor Activity of Oral Compound 1 and IV Paclitaxel**

Tumor	Expt. No.	Rt., schedule	Compound 1 (PO)			Paclitaxel (IV)
			OD <sup>1</sup> (mg/kg)	LCK <sup>2</sup> (cures/tal)	LCK <sup>2</sup>	LCK <sup>2</sup>
Pat-7	8	PO, q2dx5	60	3.1	1.3	
	9	PO, q2dx5	80	2.5	1.2	
HCT116	52	PO, q2dx5	90	>6.3 (7/8)	ND <sup>4</sup>	

<sup>1</sup> OD, optimal dose or maximum tolerated dose (MTD).  
<sup>2</sup> LCK, gross log cell kill. When 50% or greater of the treated animals are cured, LCK value is calculated based on tumor measurements of the last date prior to cure is declared and represents a minimum estimate of LCK (>). In such cases, cured rates are also described.  
<sup>3</sup> LCK are for optimal dose (dose ranged from 24-36 mg/kg), or highest dose tested if inactive.  
<sup>4</sup> ND, not done.

**Schedule Dependency**

Several studies were conducted to evaluate the schedule dependency of Compound 1. In the first study, employing the A2780 tumors, Compound 1 was administered to mice by two different schedules: (1) the traditional (optimized for paclitaxel) every 2 days x 5 schedule, and (2) the less frequent every 4 days x 3 schedule. Although both schedules were active, yielding 2.4 and >5.3 LCKs, respectively, the less frequent dosing schedule allows a higher dose level to be given (MTD = 16 mg/kg/inj) and performed far better than the more frequent schedule (MTD = 6.3 mg/kg/inj) (Figure 6 and Table 9).

In a second study, in the HCT116 human colon carcinoma model, three different schedules of treatment were used: q2dx5, q4dx3, as well as q8dx2. All treatments were IV and the tumors were staged to 100 mg at the initiation of treatment. Best results were obtained with the q8dx2 treatment schedule. At the optimal dose of 24 mg/kg/inj, Compound 1 produced 100% cures (8 of 8 mice). The q4dx3 and q2dx5 schedules yielded cures in 5 of 8 and 4 of 8 mice, respectively (Table 9).

In two other studies, employing the Pat-7 and HCT116/VM46 tumors, the efficacy of two IV treatment schedules were compared: q2dx5 and q4dx3. In both cases, the two regimens yielded essentially equivalent antitumor activities (Table 9).

30

Table 9. Schedule-dependency of the antitumor activity of Compound 1				
Tumor	Expt. No.	Compound 1		
		Rt., schedule	OD <sup>1</sup> (mg/kg)	LCK <sup>2</sup> (cures/total)
A2780	115	IV, q2dx5	6.3	2.4 (0/8)
	115	IV, q4dx3	16	>5.3 (3/7)
HCT116	52	IV, q2dx5	6.3	>6.3 (4/8)
	52	IV, q4dx3	10	>6.3 (5/8)
	52	IV, q8dx2	24	>6.3 (8/8)
Pat-7	12	IV, q2dx5	6.3	2.1
	12	IV, q4dx3	15	1.7
HCT116/VM46	35	IV, q2dx5	6.3	1.8
	35	IV, q4dx3	16	2.0
<sup>1</sup> OD, optimal dose or maximum tolerated dose (MTD). <sup>2</sup> LCK, gross log cell kill. When 50% or greater of the treated animals are cured, LCK value is calculated based on tumor measurements of the last date prior to cure is declared and represents a minimum estimate of LCK (>). In such cases, cured rates are also described.				

5

Compound 1 has clearly demonstrated antitumor activity superior to paclitaxel in five paclitaxel-resistant tumors - four human tumor xenografts and one murine tumor: the clinically-derived paclitaxel resistant Pat-7 ovarian carcinoma; the A2780Tax ovarian carcinoma that is resistant to paclitaxel because of tubulin mutation; the HCT116/VM46 MDR colon carcinoma, the clinically-derived paclitaxel-resistant Pat-21 breast carcinoma; and the murine fibrosarcoma M5076. Against three paclitaxel-sensitive human tumor xenografts Compound 1 produced antitumor activity equivalent to paclitaxel: A2780 human ovarian carcinoma; HCT116 and LS174T human colon carcinoma. In addition, Compound 1 is orally active, producing antitumor activity by the oral route that is equivalent to that produced by IV drug

administration in two different human tumor xenografts.

#### EXAMPLE 6

5        Anti-proliferative agents in combination with the  
         compounds of the invention act synergistically to kill  
         tumor cells in human tumor xenografts

Therapeutic synergism was also clearly demonstrated  
10 with the combination of Compound 1 and Compound 2 in vivo  
in the multidrug resistant human colon carcinoma  
xenografts HCT/VM46. Both Compound 1 and Compound 2 have  
modest antitumor activity in this model as a single agent  
treatment (Fig. 7). Both agents caused greater than 1  
15 LCK of tumor response (1.6 and 1.1 LCK, respectively) but  
did not induce tumor cure. However, when the two agents  
were administered in combination (Compound 1 followed 24  
hr later with Compound 2), dramatic improvement in  
antitumor activity was observed. Notably, a highly  
20 significant increase in tumor growth delay (3.7 LCK)  
including enhanced curative effects were observed in 3  
out of 7 mice (Fig. 7).

The sequence dependency of the combination was  
demonstrated. When Compound 2 treatment was administered  
25 24 h prior to Compound 1, no therapeutic synergism was  
observed (Fig. 8), with the combination performing only  
as well as Compound 1 given alone.

30

EXAMPLE 7PHARMACOLOGICAL STUDIES OF COMPOUND 1 ALONE AND IN  
COMBINATION WITH OTHER ANTI-NEOPLASTIC AGENTS IN PATIENTS  
WITH ADVANCED CANCER

5

Given the cytotoxic effects of Compound 1 both in vivo and in vitro, phase I clinical trials are underway to assess toxicity in patients with advanced cancer. Patients having peritoneal ovarian cancer, non-small cell lung carcinoma, melanoma and an unknown primary cancer were assessed for an objective response. Compound 1 was given in escalating doses which ranged from 7.4 mg/m<sup>2</sup> to 65 mg/m<sup>2</sup>. These studies revealed the MTD. The dose recommended for Phase II clinical trials is 50 mg/m<sup>2</sup> using q3 week schedule.

Compound 1 is also being assessed in Phase I studies in combination with other chemotherapeutic agents. Compound 1 will be administered at a starting dose of 30 mg/m<sup>2</sup> in combination with carboplatin at 6 AUC using q3 week schedule. Other studies are being performed to assess the efficacy of combined administration of Compound 1 at 30 mg/m<sup>2</sup> and doxorubicin at 50 mg/m<sup>2</sup> using a q3 week schedule. Combination chemotherapeutic regimens wherein Compound 1 at 30 mg/m<sup>2</sup> is combined with CPT-11 at 150 mg/m<sup>2</sup> are also underway.

Compound 1 is also being assessed in Phase II clinical studies on cancer patients who have not responded to treatment regimens using taxanes, anthracyclines, platinum, and 5 FU in combination with CPT-11. In these studies, Compound 1 will be administered using a dosing regimen consisting of 50/mg/m<sup>2</sup> intravenous infusion for 1 hour every three weeks for 18 cycles (PR and SD) or 4 cycles after CR.

## REFERENCES

1. Long BH, et al., Mechanisms of resistance to etoposide and teniposide in acquired resistant human colon and lung carcinoma cell lines. Cancer Research, 1991. **51**: 5275-5284.
2. Giannakakou P, et al., Paclitaxel-resistant human ovarian cancer cells have mutant beta-tubulins that exhibit impaired paclitaxel-driven polymerization. J. Biol. Chem., 1997. **272**(27): 17118-25.
3. Riss TL, et al. Comparison of MTT, XTT, and a novel tetrazolium compound MTS for in vitro proliferation and chemosensitivity assays. Molecular Biology of the Cell, 1992. **3 (suppl.)**: 184a.
4. Stephens TC, Steel GG. The evaluation of combinations of cytotoxic drugs and radiation: Isobolograms and therapeutic synergism. In, Rodent tumor models in experimental cancer therapy, pp. 248. Ed. Robert F. Kallman. Pergamon Press, NY.
5. Long BH, Fairchild CR. Paclitaxel inhibits progression of mitotic cells to G(1) phase by interference with spindle formation without affecting other microtubule functions during anaphase and telophase. Cancer Research, 1994. **54**(16): 4355-4361.
6. Williams, RC, Lee, JC. Preparation of tubulin from brain. Methods in Enzymology, 1982. **85**(Part D): 376-385.
7. Gehan, GA. A generalized Wilcoxon test for comparing arbitrarily singly-censored samples. Biometrika, 1985. **52**: 203-233.

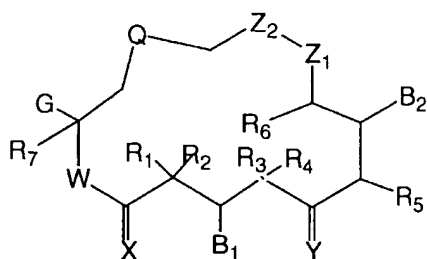
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The present invention is not limited to the embodiments specifically described above, but is capable of variation and modification without departure from the scope of the appended claims.

**What Is Claimed Is:**

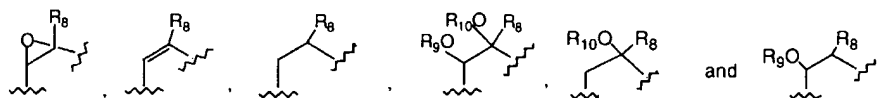
1. A method for the treatment of proliferative  
 5 diseases, including cancer, which comprises administering  
 to a mammalian specie in need thereof a synergistically,  
 therapeutically effective amount of (1) at least one  
 anti-proliferative agent(s) and 2) a compound of formula  
 I,

10



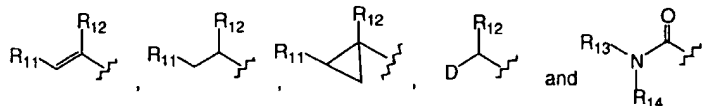
wherein:

- 15 Q is selected from the group consisting of



G is selected from the group consisting of alkyl,  
 substituted alkyl, aryl, substituted aryl, heterocyclo,

20



W is O or N R<sub>15</sub>;

X is O or H, H;

- Y is selected from the group consisting of O; H, OR<sub>16</sub>  
 25 ; OR<sub>17</sub>, OR<sub>17</sub>; NOR<sub>18</sub>; H, NHOR<sub>19</sub>; H, NR<sub>20</sub>R<sub>21</sub>; H, H; and CHR<sub>22</sub>;  
 wherein OR<sub>17</sub>, OR<sub>17</sub> can be a cyclic ketal;

Z<sub>1</sub> and Z<sub>2</sub> are independently selected from the group



consisting of CH<sub>2</sub>, O, NR<sub>23</sub>, S, and SO<sub>2</sub>, wherein only one of Z<sub>1</sub> and Z<sub>2</sub> can be a heteroatom;

B<sub>1</sub> and B<sub>2</sub> are independently selected from the group consisting of OR<sub>24</sub>, OCOR<sub>25</sub>, and O-C(=O)-NR<sub>26</sub>R<sub>27</sub>, and when B<sub>1</sub> is H and Y is OH, H, they can form a six-membered ring ketal or acetal;

D is selected from the group consisting of NR<sub>28</sub>R<sub>29</sub>, NR<sub>30</sub>COR<sub>31</sub> and saturated heterocycle;

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>13</sub>, R<sub>14</sub>, R<sub>18</sub>, R<sub>19</sub>, R<sub>20</sub>, R<sub>21</sub>, R<sub>22</sub>, R<sub>26</sub> and R<sub>27</sub> are independently selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and when R<sub>1</sub> and R<sub>2</sub> are alkyl can be joined to form a cycloalkyl, and when R<sub>3</sub> and R<sub>4</sub> are alkyl can be joined to form a cycloalkyl;

R<sub>9</sub>, R<sub>10</sub>, R<sub>16</sub>, R<sub>17</sub>, R<sub>24</sub>, R<sub>25</sub> and R<sub>31</sub> are independently selected from the group consisting of H, alkyl, and substituted alkyl;

R<sub>8</sub>, R<sub>11</sub>, R<sub>12</sub>, R<sub>28</sub>, R<sub>30</sub>, R<sub>32</sub>, and R<sub>33</sub> are independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl and heterocyclo;

R<sub>15</sub>, R<sub>23</sub> and R<sub>29</sub> are independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo, R<sub>32</sub>C=O, R<sub>33</sub>SO<sub>2</sub>, hydroxy, O-alkyl or O-substituted alkyl; and

pharmaceutically acceptable salts thereof and any hydrates, solvates or geometric, optical and stereoisomers thereof;

with the proviso that compounds wherein

W and X are both O; and

R<sub>1</sub>, R<sub>2</sub> and R<sub>7</sub> are H; and

R<sub>3</sub>, R<sub>4</sub> and R<sub>6</sub> are methyl; and

R<sub>8</sub> is H or methyl; and

Z<sub>1</sub> and Z<sub>2</sub> are CH<sub>2</sub>; and

G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl;

and

Q is as defined above  
are excluded.

- 5    2.    The method according to Claim 1 wherein the  
antiproliferative agent is administered following  
administration of the Formula I compound.
3.    The method according to Claim 1, wherein the  
10 antiproliferative agent is administered prior to the  
administration of the Formula I compound.
4.    The method according to Claim 1 wherein the  
15 antiproliferative agent is administered simultaneously  
with the formula 1 compound.
5.    The method according to Claim 1 for the treatment of  
cancerous solid tumors.  
20
6.    The method according to Claim 1 for the treatment of  
refractory tumors.
7.    The method according to Claim 1 wherein the anti-  
25 proliferative agent is selected from the group consisting  
of a microtubule-stabilizing agent, a microtubule-  
disruptor agent, an alkylating agent, an anti-metabolite,  
epidophyllotoxin, an antineoplastic enzyme, a  
topoisomerase inhibitor, procarbazine, mitoxantrone,  
30 inhibitors of cell cycle progression, radiation and a  
platinum coordination complex.
8.    The method according to Claim 1 wherein the anti-  
proliferative agent is selected from the group consisting  
35 of an anthracycline drug, a vinca drug, a mitomycin, a

bleomycin, a cytotoxic nucleoside, a taxane, an epothilone, discodermolide, a pteridine drug, a diynene, an aromatase inhibitor and a podophyllotoxin.

5 9. The method according to Claim 1, wherein the Compound of Formula I is [1S-1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-  
10 proliferative agent is Compound 2.

10. The method according to Claim 2, wherein the Compound of Formula I is [1S-1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
15 8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 2.

20 11. The method according to Claim 1, wherein the Compound of Formula I is [1S-1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-  
25 oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 3.

12. The method according to Claim 2 wherein said compound of Formula I is [1S-  
30 1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 3.

35

13. The method according to Claim 1 wherein said compound of Formula I is [1S 1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 5.

14. The method according to Claim 2 wherein said compound of Formula I is [1S 1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 5.

15. The method according to Claim 1, wherein said compound of Formula I is [1S 1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*, 16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Cisplatin.

16. The method according to Claim 3, wherein said compound of Formula I is [1S 1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*, 16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Cisplatin.

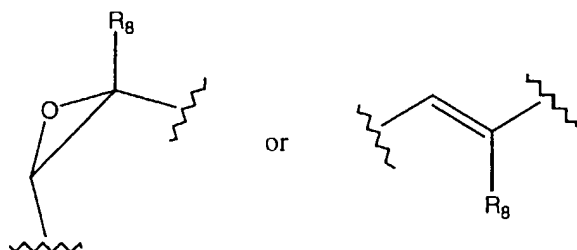
17. The method according to Claim 1, wherein said method comprises the administration of Compound 1 and Carboplatin.

18. The method according to Claim 1, wherein said method

comprises the administration of Compound 1 and doxorubicin.

19. The method according to claim 1, said method  
5 comprising the administration of Compound 1 and CPT-11.

20. The method according to claim 1, wherein Q in said Formula I compound is



10

X is O;

Y is O;

Z<sub>1</sub> and Z<sub>2</sub> are, independently, CH<sub>2</sub>; and

W is NR<sub>15</sub>.

15

21. The method according to Claim 6, wherein said compound of Formula I is selected from the group consisting of:

20 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

25 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

30 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-

- pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,10-dioxa-13-cyclohexadecene-2,6-dione;
- 5 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,10-dioxa-13-cyclohexadecene-2,6-dione;
- 10 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 15 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 20 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione;
- 25 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione;
- 30 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;
- 35 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-

- 8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;
- 5 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-3,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 10 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-3,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 15 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13,16-hexamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;
- [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,16-
- 20 pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-
- 25 thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-6,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-
- 30 thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-
- 35 thiazolyl)ethenyl]-4-aza-17-

- oxabicyclo[14.1.0]heptadecane-5,9-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-  
5 thiazolyl)ethenyl]-4-aza-17-  
oxabicyclo[14.1.0]heptadecane-5,9-dione;
- [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-  
pentamethyl-16-[1-methyl-2-(2-methyl- 4-  
10 thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;
- [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-  
tetramethyl-16-[1-methyl-2-(2-methyl- 4-  
15 thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
4,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-4-aza-17-  
oxabicyclo[14.1.0]heptadecane-5,9-dione;
- 20 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
4,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-4-aza-17-  
oxabicyclo[14.1.0]heptadecane-5,9-dione;
- 25 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-  
1,5,5,7,9,13-hexamethyl-16-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;
- 30 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-1,5,5,7,9-  
pentamethyl-16-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;
- 35 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-



thiazolyl)ethenyl]-13-aza-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
5 8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-13-aza-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-  
10 pentamethyl-16-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-  
dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-  
15 tetramethyl-16-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-  
dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
20 8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-14-aza-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
25 8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-14-aza-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-  
30 pentamethyl-16-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-  
dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-  
35 tetramethyl-16-[1-methyl-2-(2-methyl- 4-

thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione;

5 [1S-[1R\*,3R\*,7R\*,10S\*,11R\*,12R\*,16S\*]]-N-phenyl-7,11-dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

10 [1S-[1R\*,3R\*,7R\*,10S\*,11R\*,12R\*,16S\*]]-N-phenyl-7,11-dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;  
[4S-[4R\*,7S\*,8R\*,9R\*,15R\*]]-N-phenyl-4,8-dihydroxy-5,5,7,9,13-pentamethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;

15 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*]]-N-phenyl-4,8-dihydroxy-5,5,7,9-tetramethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;

20 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)cyclopropyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)cyclopropyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione; and

30 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-hydroxymethyl-4-thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione; and pharmaceutically acceptable salts, solvates and hydrates thereof.

22. The method as claimed in Claim 7, wherein said Compound of Formula I is selected from the group consisting of:

- 5 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 10 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 15 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,10-dioxo-13-cyclohexadecene-2,6-dione;
- 20 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,10-dioxo-13-cyclohexadecene-2,6-dione;
- 25 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 30 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 35 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-

- pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione;
- 5 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione;
- 10 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;
- 15 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;
- 20 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-3,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 25 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-3,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 30 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13,16-hexamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;
- 35 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,16-pentamethyl-16-[1-methyl-2-(2-methyl- 4-

thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-  
5 thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-  
5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
6,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-  
10 thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-  
5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-  
15 thiazolyl)ethenyl]-4-aza-17-  
oxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-  
20 thiazolyl)ethenyl]-4-aza-17-  
oxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-  
pentamethyl-16-[1-methyl-2-(2-methyl- 4-  
25 thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-  
tetramethyl-16-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

30

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
4,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-4-aza-17-  
oxabicyclo[14.1.0]heptadecane-5,9-dione;

35

- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-4,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;
- 5 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-1,5,5,7,9,13-hexamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;
- 10 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-1,5,5,7,9-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-15 8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-13-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-20 8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-13-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-25 pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-dione;
- [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-30 tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-35 8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-

thiazolyl)ethenyl]-14-aza-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
5 8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-14-aza-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-  
10 pentamethyl-16-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-  
dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-  
15 tetramethyl-16-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-  
dione;

[1S-[1R\*,3R\*,7R\*,10S\*,11R\*,12R\*,16S\*]]-N-phenyl-7,11-  
20 dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-  
dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

[1S-[1R\*,3R\*,7R\*,10S\*,11R\*,12R\*,16S\*]]-N-phenyl-7,11-  
dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-  
25 dioxabicyclo[14.1.0]heptadecane-3-carboxamide;  
[4S-[4R\*,7S\*,8R\*,9R\*,15R\*]]-N-phenyl-4,8-dihydroxy-  
5,5,7,9,13-pentamethyl-2,6-dioxo-1-oxa-13-  
cyclohexadecene-16-carboxamide;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*]]-N-phenyl-4,8-dihydroxy-  
5,5,7,9-tetramethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-  
16-carboxamide;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
35 8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-

thiazolyl)cyclopropyl]-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
5 8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)cyclopropyl]-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione; and

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-  
10 pentamethyl-16-[1-methyl-2-(2-hydroxymethyl- 4-  
thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione;  
and pharmaceutically acceptable salts, solvates and  
hydrates thereof.

15 23. A pharmaceutical composition for the treatment  
of cancer which comprises at least one anti-proliferative  
agent and a compound of Formula I as described in Claim  
1, and a pharmaceutically acceptable carrier.

20 24. The composition according to Claim 23 for the  
treatment of cancerous solid tumors.

25. The composition according to Claim 23 for the  
treatment of refractory tumors.

25

26. The composition according to Claim 23 wherein the  
antiproliferative agent is one or more agent selected  
from the group consisting of a microtubule-stabilizing  
agent, a microtubule-disruptor agent, an alkylating  
30 agent, an anti-metabolite, epidophyllotoxin, an  
antineoplastic enzyme, a topoisomerase inhibitor,  
procarbazine, mitoxantrone, inhibitors of cell cycle  
progression, a platinum coordination complex, an  
anthracycline drug, a vinca drug, CDK inhibitors, a  
35 mitomycin, a bleomycin, a cytotoxic nucleoside, a taxane,



compound 2, compound 3, an epothilone, discodermolide, a pteridine drug, a diynene, an aromatase inhibitor and a podophyllotoxin.

- 5 27. The composition according to Claim 23 wherein the compound of Formula I is selected from the group consisting of [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,13,17-
- 10 trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,13,17-
- 15 trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,10-dioxa-13-cyclohexadecene-2,6-
- 20 dione;
- [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,10-dioxa-13-cyclohexadecene-2,6-
- 25 dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,14,17-
- 30 trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,14,17-
- 35 trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,11-dioxo-13-cyclohexadecene-2,6-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,11-dioxo-13-cyclohexadecene-2,6-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-3,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-3,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13,16-hexamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;

- [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,16-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;
- 5 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 10 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-6,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 15 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;
- 20 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;
- 25 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;
- [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-
- 30 tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;
- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-
- 4,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl- 4-
- 35 thiazolyl)ethenyl]-4-aza-17-

oxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
4,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-  
5 thiazolyl)ethenyl]-4-aza-17-  
oxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-  
1,5,5,7,9,13-hexamethyl-16-[1-methyl-2-(2-methyl- 4-  
10 thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-1,5,5,7,9-  
pentamethyl-16-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

15 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-13-aza-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

20 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-13-aza-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-  
pentamethyl-16-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-  
dione;

30 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-  
tetramethyl-16-[1-methyl-2-(2-methyl- 4-  
thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-  
dione;

35

- [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-14-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 5 [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-14-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 10 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione;
- 15 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione;
- 20 [1S-[1R\*,3R\*,7R\*,10S\*,11R\*,12R\*,16S\*]]-N-phenyl-7,11-dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;
- 25 [1S-[1R\*,3R\*,7R\*,10S\*,11R\*,12R\*,16S\*]]-N-phenyl-7,11-dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;
- 30 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*]]-N-phenyl-4,8-dihydroxy-5,5,7,9,13-pentamethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;
- 35 [4S-[4R\*,7S\*,8R\*,9R\*,15R\*]]-N-phenyl-4,8-dihydroxy-5,5,7,9-tetramethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)cyclopropyl]-4,17-  
5 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-  
thiazolyl)cyclopropyl]-4,17-  
10 dioxabicyclo[14.1.0]heptadecane-5,9-dione; and :

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-4,8-dihydroxy-5,5,7,9,13-  
pentamethyl-16-[1-methyl-2-(2-hydroxymethyl- 4-  
thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione;  
15 and pharmaceutically acceptable salts, solvates and  
hydrates thereof.

28. The composition according to Claim 26 wherein the  
20 pharmaceutically acceptable salt is selected from the  
group consisting of the hydrochloride salt, the  
methanesulfonic acid salt and the trifluoroacetic acid  
salt.

25 29. The composition according to Claim 26 wherein the  
formula I compound is [1S-  
1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-  
thiazolyl)ethenyl]-4-aza-17-  
30 oxabicyclo[14.1.0]heptadecane-5,9-dione or a  
pharmaceutically acceptable salt thereof and the anti-  
proliferative agent is Compound 2.

30. The composition according to Claim 26 wherein the  
35 antiproliferative agent is Compound 3 and the formula I

compound is [1S 1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*, 16S\*]]-  
7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-  
methyl-4-thiazolyl)ethenyl]-4-aza-17-  
oxabicyclo[14.1.0]heptadecane-5,9-dione or a  
5 pharmaceutically acceptable salt thereof.

31. The composition according to Claim 26 wherein the  
antiproliferative agent is Compound 5 and the formula I  
compound is [1S 1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*, 16S\*]]-  
10 7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-  
methyl-4-thiazolyl)ethenyl]-4-aza-17-  
oxabicyclo[14.1.0]heptadecane-5,9-dione or a  
pharmaceutically acceptable salt thereof.

15 32. The composition according to claim 26 wherein the  
antiproliferative agent is cisplatin and the compound of  
formula I is [1S 1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-  
7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-  
methyl-4-thiazolyl)ethenyl]-4-aza-17-  
20 oxabicyclo[14.1.0]heptadecane-5,9-dione.

33. The composition according to claim 23, wherein said  
composition comprises Compound 1 and carboplatin.

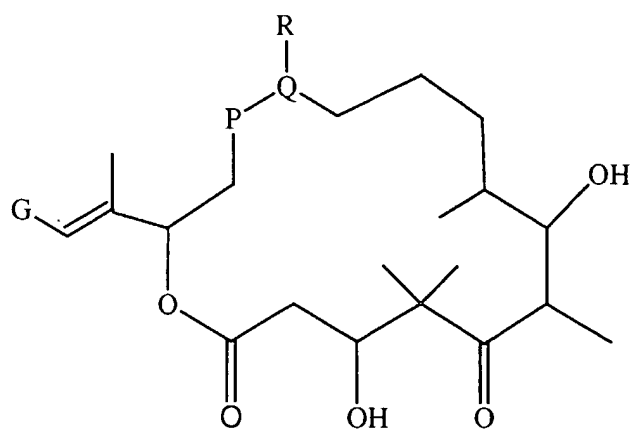
25 34. The composition according to claim 23, wherein said  
composition comprises Compound 1 and doxorubicin.

35. The composition according to claim 23, wherein said  
composition comprises Compound 1 and CPT-11.

30

36. A method for the treatment of proliferative  
diseases, including cancer, which comprises administering  
to a mammalian specie in need thereof a synergistically,  
therapeutically effective amount of (1) at least one  
35 anti-proliferative agent(s) and (2) a compound of Formula

II:

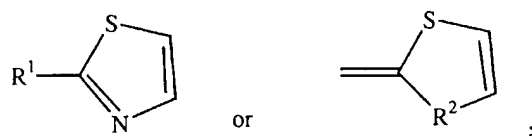


5

wherein:

P-Q is a C, C double bond or an epoxide;

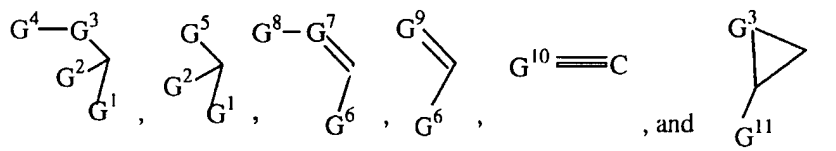
G is



10

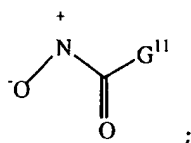
R is selected from the group of H, alkyl, and substituted alkyl;

R¹ is selected from the group consisting of



15

R² is



G¹ is selected from the group of H, halogen, CN, alkyl and substituted alkyl;

G² is selected from the group of H, alkyl, and



substituted alkyl;

$G^3$  is selected from the group of O, S, and  $NZ^1$ ;

$G^4$  is selected from the group of H, alkyl, substituted alkyl,  $OZ^2$ ,  $NZ^2Z^3$ ,  $Z^2C=O$ ,  $Z^4SO_2$ , and optionally

5 substituted glycosyl;

$G^5$  is selected from the group of halogen,  $N_3$ , NCS, SH, CN, NC,  $N(Z^1)_3^+$  and heteroaryl;

$G^6$  is selected from the group of H, alkyl, substituted alkyl,  $CF_3$ ,  $OZ^5$ ,  $SZ^5$ , and  $NZ^5Z^6$ ;

10  $G^7$  is  $CZ^7$  or N;

$G^8$  is selected from the group of H, halogen, alkyl, substituted alkyl,  $OZ^{10}$ ,  $SZ^{10}$ ,  $NZ^{10}Z^{11}$ ;

$G^9$  is selected from the group of O, S, -NH-NH- and -N=N-;

15  $G^{10}$  is N or  $CZ^{12}$ ;

$G^{11}$  is selected from the group of  $H_2N$ , substituted  $H_2N$ , alkyl, substituted alkyl, aryl, and substituted aryl;

$Z^1$ ,  $Z^6$ ,  $Z^9$ , and  $Z^{11}$  are independently selected from the group H, alkyl, substituted alkyl, acyl, and

20 substituted acyl;

$Z^2$  is selected from the group of H, alkyl, substituted alkyl, aryl, substituted aryl, and heterocycle;

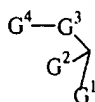
$Z^3$ ,  $Z^5$ ,  $Z^8$ , and  $Z^{10}$  are independently selected from  
25 the group H, alkyl, substituted alkyl, acyl, substituted acyl, aryl, and substituted aryl;

$Z^4$  is selected from the group of alkyl, substituted alkyl, aryl, substituted aryl, and heterocycle;

$Z^7$  is selected from the group of H, halogen, alkyl, substituted alkyl, aryl, substituted aryl,  $OZ^8$ ,  $SZ^8$ , and  
30  $NZ^8Z^9$ ; and

$Z^{12}$  is selected from the group of H, halogen, alkyl, substituted alkyl, aryl, and substituted aryl;

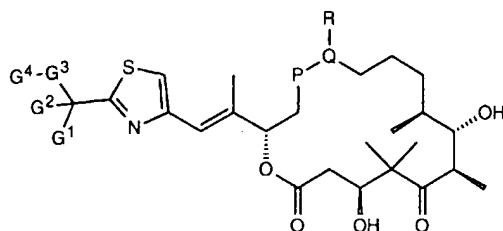
with the proviso that when  $R^1$  is



$G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  cannot simultaneously have the following meanings:

$G^1$  and  $G^2 = H$ ,  $G^3 = O$  and  $G^4 = H$  or  $Z^2C=O$  where  $Z^2 =$   
 5 alkyl group.

37. The method according to Claim 36 wherein the  
 10 compound has the general formula IIa



where the symbols have the following meaning:

P-Q is a C,C double bond or an epoxide,

15 R is a H atom or a methyl group,

$G^1$  is an H atom, an alkyl group, a substituted alkyl group or a halogen atom,

$G^2$  is an H atom, an alkyl group or a substituted alkyl group,

20  $G^3$  is an O atom, an S atom or an  $NZ^1$  group with  $Z^1$  being an H atom, an alkyl group, a substituted alkyl group, an acyl group, or a substituted acyl group, and

$G^4$  is an H atom, an alkyl group, a substituted alkyl group, an  $OZ^2$  group, an  $NZ^2Z^3$  group, a  $Z^2C=O$  group, a  $Z^4SO_2$   
 25 group or an optionally substituted glycosyl group with  $Z^2$  being a H atom, an alkyl group, a substituted alkyl group, an aryl group, a substituted aryl group or a heterocyclic group,

Z<sup>3</sup> an H atom, an alkyl group, a substituted alkyl group, an acyl group or a substituted acyl group, and Z<sup>4</sup> an alkyl, a substituted alkyl, an aryl, a substituted aryl or a heterocyclic group,

5

with the proviso that G<sup>1</sup>, G<sup>2</sup>, G<sup>3</sup> and G<sup>4</sup> cannot have simultaneously the following meanings: G<sup>1</sup> and G<sup>2</sup> = H atom, G<sup>3</sup> = O atom and G<sup>4</sup> = H atom or Z<sup>2</sup>C=O with Z<sup>2</sup> = alkyl group.

10 38. The method of claim 36 wherein said compound of Formula II is [1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.

15

39. The method according to Claim 36, wherein the antiproliferative agent is administered following administration of the Formula II compound.

20 40. The method according to Claim 36, wherein the antiproliferative agent is administered prior to administration of the Formula II compound.

41. The method according to Claim 36, wherein the  
25 antiproliferative agent is administered simultaneously with the Formula II compound.

42. The method according to Claim 36 for the treatment of cancerous solid tumors.

30

43. The method according to Claim 36 for the treatment of refractory tumors.

44. The method according to Claim 36 wherein the anti-  
35 proliferative agent is selected from the group consisting

of a microtubule-stabilizing agent, a microtubule-disruptor agent, an alkylating agent, an anti-metabolite, epidophyllotoxin, an antineoplastic enzyme, a topoisomerase inhibitor, procarbazine, mitoxantrone,  
5 radiation, a platinum coordination complex, anthracycline drug, a vinca drug, a mitomycin, inhibitors of cell cycle progression, a bleomycin, a cytotoxic nucleoside, a taxane, an epothilone, discodermolide, a pteridine drug, a diynene, an aromatase inhibitor and a podophyllotoxin.

10

45. The method according to Claim 37 wherein the anti-proliferative agent is selected from the group consisting of a microtubule-stabilizing agent, a microtubule-disruptor agent, an alkylating agent, an anti-metabolite,  
15 epidophyllotoxin, an antineoplastic enzyme, a topoisomerase inhibitor, procarbazine, mitoxantrone, radiation, a platinum coordination complex, anthracycline drug, a vinca drug, a mitomycin, inhibitors of cell cycle progression, a bleomycin, a cytotoxic nucleoside, a  
20 taxane, an epothilone, discodermolide, a pteridine drug, a diynene, an aromatase inhibitor and a podophyllotoxin.

46. The method according to Claim 36, wherein the Compound of Formula II is 1S-  
25 [1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 2.

30

47. The method according to Claim 37, wherein the Compound of Formula II is 1S-  
[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-  
35 dihydroxy-8,8,10,12,16-pentamethyl-4,17-

dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 2.

48. The method according to Claim 36 wherein said  
5 compound of Formula II is 1S-  
[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-  
(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-  
dihydroxy-8,8,10,12,16-pentamethyl-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-  
10 proliferative agent is Compound 3.

49. The method according to Claim 37 wherein said  
compound of Formula II is 1S-  
[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-  
15 (Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-  
dihydroxy-8,8,10,12,16-pentamethyl-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-  
proliferative agent is Compound 3.

20 50. The method according to Claim 36, wherein said  
compound of Formula II is 1S-  
[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-  
(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-  
dihydroxy-8,8,10,12,16-pentamethyl-4,17-  
25 dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-  
proliferative agent is Cisplatin.

51. The method according to Claim 37, wherein said  
compound of Formula II is 1S-  
30 [1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-  
(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-  
dihydroxy-8,8,10,12,16-pentamethyl-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-  
proliferative agent is Cisplatin.

35

52. The method according to Claim 36, wherein said compound of Formula II is 1S-  
[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-  
5 dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 5.

53. The method according to Claim 37, wherein said  
10 compound of Formula II is 1S-  
[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-  
15 proliferative agent is Compound 5.

54. The method according to Claim 36, wherein said method comprises the administration of Compound 4 and Carboplatin.

20

55. The method according to Claim 37, wherein said method comprises the administration of Compound 4 and Carboplatin.

25 56. The method according to Claim 36, wherein said method comprises the administration of Compound 4 and doxorubicin.

57. The method according to Claim 37, wherein said method  
30 comprises the administration of Compound 4 and doxorubicin

58. The method according to Claim 36, wherein said compound of Formula II is selected from the group  
35 consisting of

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Azidomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-[[[(1,1-Dimethylethoxy) carbonyl] amino] methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-16-[2-[2-[[[(1,1-Dimethylethoxy) carbonyl] amino] methyl]-4-thiazolyl]-1-methyl-ethenyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-1-oxa-13(Z)-cyclohexadecene-2,6-dione;

20

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-16-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-1-oxa-13(Z)-cyclohexadecene-2,6-dione;

25

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(pentanoyloxy) methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(naphthoyloxy) methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

35

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-3-[2-[2-[[2-methoxyethoxy]acetyloxy]methyl]-1-methyl-4-thiazolyl]ethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(N-propionylamino)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(3-Acetyl-2,3-dihydro-2-methylene-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione, N-oxide;

15

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-3-[2-[2-(methoxymethyl)-4-thiazolyl]-1-methylethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

20

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-(phenoxymethyl)-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-[(Ethylthio)methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Ethoxymethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

35



[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(2,3,4,6-  
tetraacetyl-alpha-glucosyloxy)methyl]-4-  
thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-  
5 5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(2',3',4',6'-  
tetraacetyl-beta-glucosyloxy)methyl]-4-  
10 thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-  
5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(6'-acetyl-alpha-  
15 glucosyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(p-  
20 toluenesulfonyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-  
(Bromomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-  
25 dihydroxy-8,8,10,12-tetramethyl-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(5-Bromo-  
2-methyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-  
30 8,8,10,12-tetramethyl-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-  
(Cyanomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-  
35 dihydroxy-8,8,10,12,16-pentamethyl-4,17-

dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-16-[2-[2-(Cyanomethyl)-4-thiazolyl]-1-methylethenyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-1-oxa-13(Z)-cyclohexadecene-2,6-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-3-[2-[2-(1H-imidazol-1-ylmethyl)-4-thiazolyl]-1-methylethenyl]-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Formyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Formyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Ethenyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-3-[2-[2-(methoxyimino)-4-thiazolyl]-1-methylethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[[ (phenylmethyl)imino]methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Acetyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-oxiranyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-3-[2-[2-(2-iodoethenyl)-4-thiazolyl]-1-methylethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Ethynyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(methylamino)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-[[2-(Dimethylamino)ethyl]amino]methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-[(Dimethylamino)methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-  
 [[Bis(2-methoxyethyl)amino]methyl]-4-thiazolyl]-1-  
 methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-  
 5 4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
 8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(4-methyl-1-  
 piperazinyl)methyl]-4-thiazolyl]ethenyl]-4,17-  
 10 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-4-[2-(7,11-  
 Dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-  
 dioxabicyclo[14.1.0]heptadecan-3-yl)-1-propenyl]-2-  
 15 thiazolecarboxylic acid;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-4-[2-(7,11-  
 Dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-  
 dioxabicyclo[14.1.0]heptadecan-3-yl)-1-propenyl]-2-  
 20 thiazolecarboxylic acid methyl ester;  
 and the pharmaceutically acceptable salts, solvents and  
 hydrates thereof.

59. A pharmaceutical composition for the pharmaceutical  
 25 treatment of cancer with which comprises at least one  
 anti-proliferative agent and a compound of Formula II as  
 described in Claim 36, and a pharmaceutically acceptable  
 carrier.

60. The composition according to Claim 59 for the treatment of cancerous solid tumors.

61. The composition according to Claim 59 for the treatment of refractory tumors.

62. The composition according to Claim 59 wherein the antiproliferative agent is one or more agent selected from the group consisting of a microtubule-stabilizing agent, a microtubule-disruptor agent, an alkylating agent, an anti-metabolite, epidophyllotoxin, an antineoplastic enzyme, a topoisomerase inhibitor, procarbazine, mitoxantrone, a platinum coordination complex, an anthracycline drug, a cell cycle progression inhibitor, a vinca drug, a mitomycin, a bleomycin, a cytotoxic nucleoside, a taxane, Compound 2, Compound 3, Compound 5, an epothilone, discodermolide, a pteridine drug, a diynene, an aromatase inhibitor and a podophyllotoxin.

20

63. The composition according to Claim 59, wherein the compound of Formula II is selected from the group consisting of

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Azidomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-  
[[[(1,1-Dimethylethoxy)carbonyl]amino]methyl]-4-  
thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-  
pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-  
5 dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-16-[2-[2-[[[(1,1-  
Dimethylethoxy)carbonyl]amino]methyl]-4-thiazolyl]-1-  
methyl-ethenyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-1-  
10 oxa-13(Z)-cyclohexadecene-2,6-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-16-[2-[2-(Aminomethyl)-4-  
thiazolyl]-1-methylethenyl]-4,8-dihydroxy-5,5,7,9,13-  
pentamethyl-1-oxa-13(Z)-cyclohexadecene-2,6-dione;  
15

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-[2-  
[(pentanoyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
20

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-[2-  
[(naphthoyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
25

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
3-[2-[2-[[2-methoxyethoxy]acetyloxy]methyl]-1-methyl-4-  
thiazolyl]ethenyl]-8,8,10,12-tetramethyl-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
30

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(N-  
propionylamino)methyl]-4-thiazolyl]ethenyl]-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;  
35

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(3-Acetyl-  
2,3-dihydro-2-methylene-4-thiazolyl)-1-methylethenyl]-  
7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione, N-oxide;

5

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
3-[2-[2-(methoxymethyl)-4-thiazolyl]-1-methylethenyl]-  
8,8,10,12-tetramethyl-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-  
(phenoxymethyl)-4-thiazolyl]ethenyl]-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-  
[(Ethylthio)methyl]-4-thiazolyl]-1-methylethenyl]-7,11-  
dihydroxy-8,8,10,12,16-pentamethyl-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

20

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-  
(Ethoxymethyl)-4-thiazolyl]-1-methylethenyl]-7,11-  
dihydroxy-8,8,10,12-tetramethyl-4,17-  
dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(2,3,4,6-  
tetraacetyl-alpha-glucosyloxy)methyl]-4-  
thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-

30

5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(2',3',4',6'-  
tetraacetyl-beta-glucosyloxy)methyl]-4-  
thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-  
5 5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[(6'-acetyl-alpha-  
glucosyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-  
10 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-  
8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(p-  
toluenesulfonyloxy)methyl]-4-thiazolyl]ethenyl]-4,17-  
15 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-  
(Bromomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-  
dihydroxy-8,8,10,12-tetramethyl-4,17-  
20 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(5-Bromo-  
2-methyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-  
8,8,10,12-tetramethyl-4,17-  
25 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-  
(Cyanomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-  
dihydroxy-8,8,10,12,16-pentamethyl-4,17-  
30 dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R\*,7S\*,8R\*,9R\*,15R\*(E)]]-16-[2-[2-(Cyanomethyl)-4-  
thiazolyl]-1-methylethenyl]-4,8-dihydroxy-5,5,7,9,13-  
pentamethyl-1-oxa-13(Z)-cyclohexadecene-2,6-dione;  
35



{1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]}-7,11-Dihydroxy-3-[2-[2-(1H-imidazol-1-ylmethyl)-4-thiazolyl]-1-methylethenyl]-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

{1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]}-3-[2-(2-Formyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10

{1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]}-3-[2-(2-Formyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15

{1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]}-3-[2-(2-Ethenyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

20

{1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]}-7,11-Dihydroxy-3-[2-[2-(methoxyimino)-4-thiazolyl]-1-methylethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25

{1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]}-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-[2-[[ (phenylmethyl)imino]methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30

{1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]}-3-[2-(2-Acetyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

35

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-oxiranyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-3-[2-[2-(2-iodoethenyl)-4-thiazolyl]-1-methylethenyl]-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-(2-Ethynyl-4-thiazolyl)-1-methylethenyl]-7,11-dihydroxy-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(methylamino)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

20

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-[[2-(Dimethylamino)ethyl]amino]methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-[(Dimethylamino)methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-[[Bis(2-methoxyethyl)amino]methyl]-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

35

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-[2-[(4-methyl-1-piperazinyl)methyl]-4-thiazolyl]ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-4-[2-(7,11-Dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecan-3-yl)-1-propenyl]-2-thiazolecarboxylic acid;

10

[1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-4-[2-(7,11-Dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecan-3-yl)-1-propenyl]-2-thiazolecarboxylic acid methyl ester

15 and the pharmaceutically acceptable salts, solvents and hydrates thereof.

64. The composition according to Claim 59 wherein the compound of Formula II is selected from the group

20 consisting of

1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-

25 proliferative agent is Compound 2.

65. The composition according to Claim 59 wherein the compound of Formula II is selected from the group consisting of

30 1S-[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 3.

35

66. The composition according to Claim 59 wherein said compound of Formula II is 1S-  
[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-  
5 dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-proliferative agent is Compound 5.

67. The composition according to Claim 59, wherein said  
10 compound of Formula II is 1S-  
[1R\*,3R\*(E),7R\*,10S\*,11R\*,12R\*,16S\*]]-3-[2-[2-(Aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-  
15 proliferative agent is Cisplatin.

68. The composition according to Claim 59, wherein said composition comprises Compound 4 and Carboplatin.

20 69. The composition according to Claim 59, wherein said method comprises the administration of Compound 4 and doxorubicin.

70. The composition according to Claim 59, wherein said  
25 method comprises the administration of Compound 4 and CPT-11.

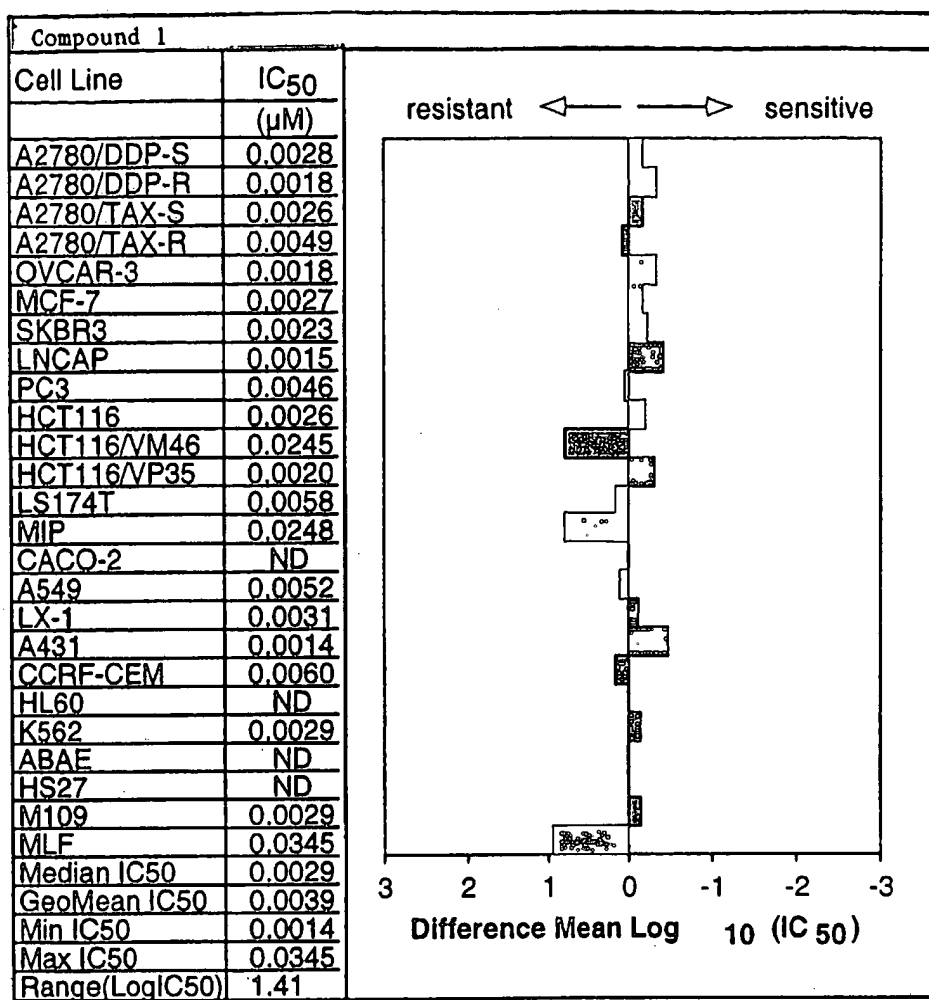


Figure 1

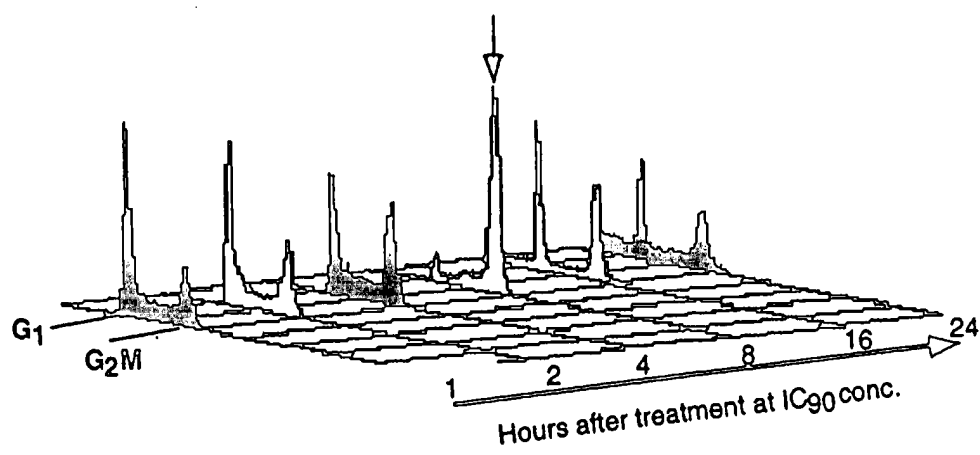


Figure 2

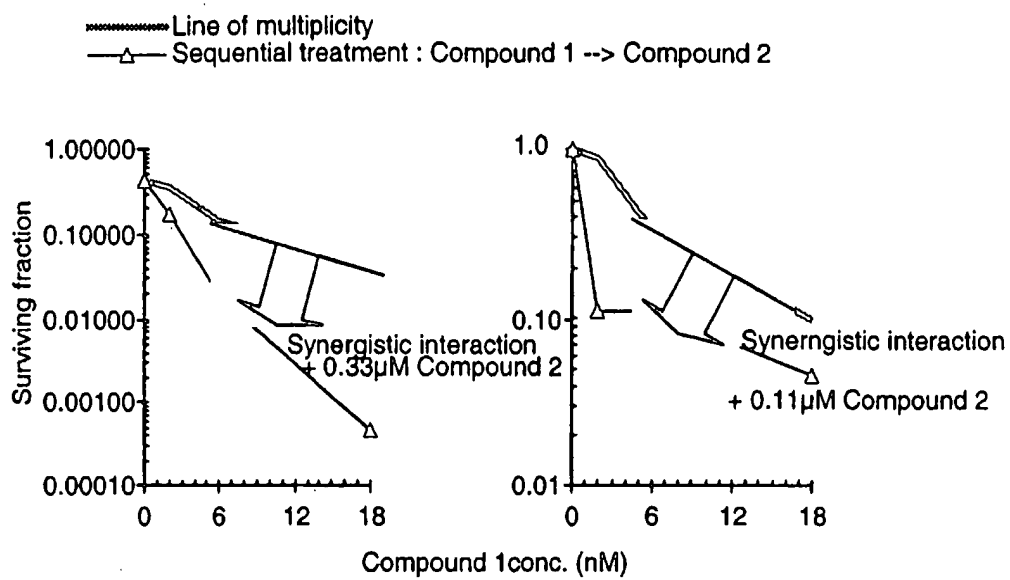


Figure 3A

Figure 3B

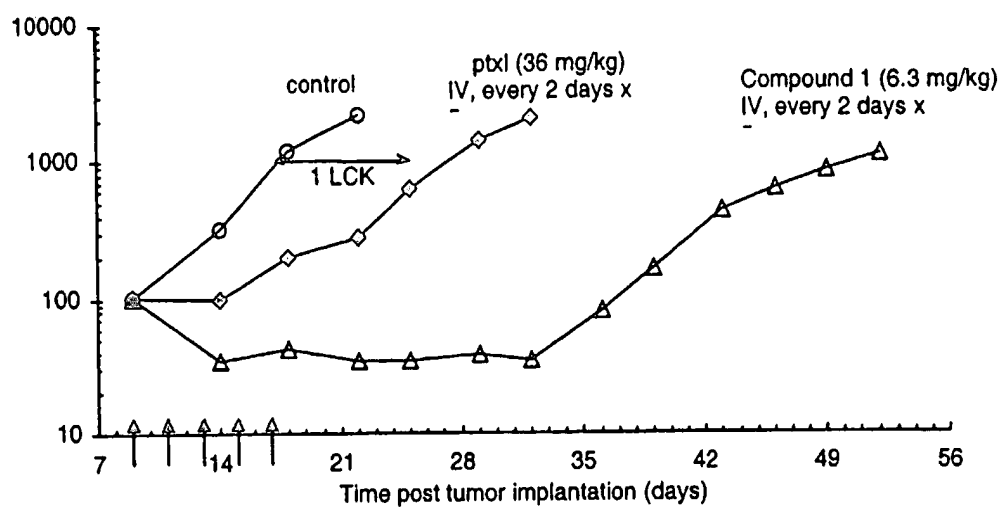


Figure 4



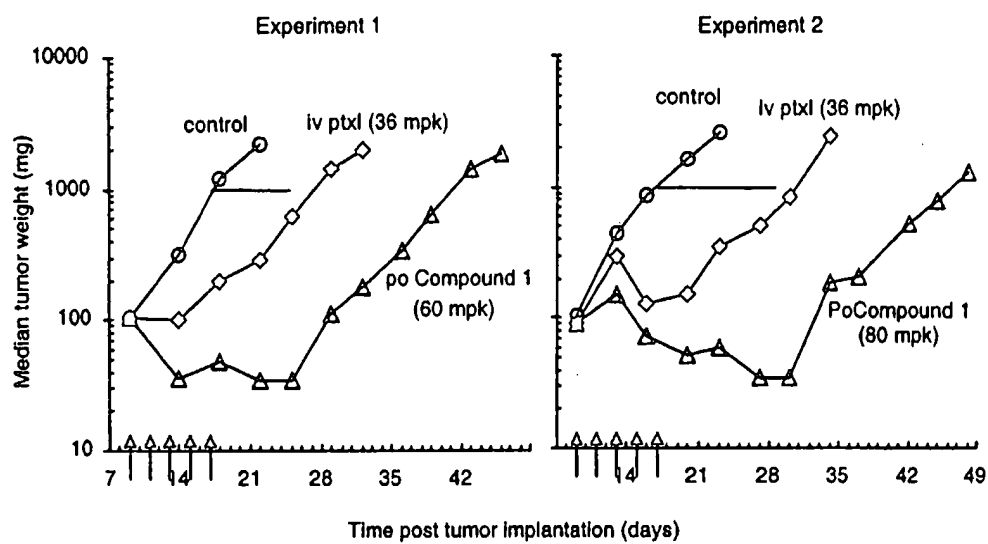


Figure 5A

Figure 5B

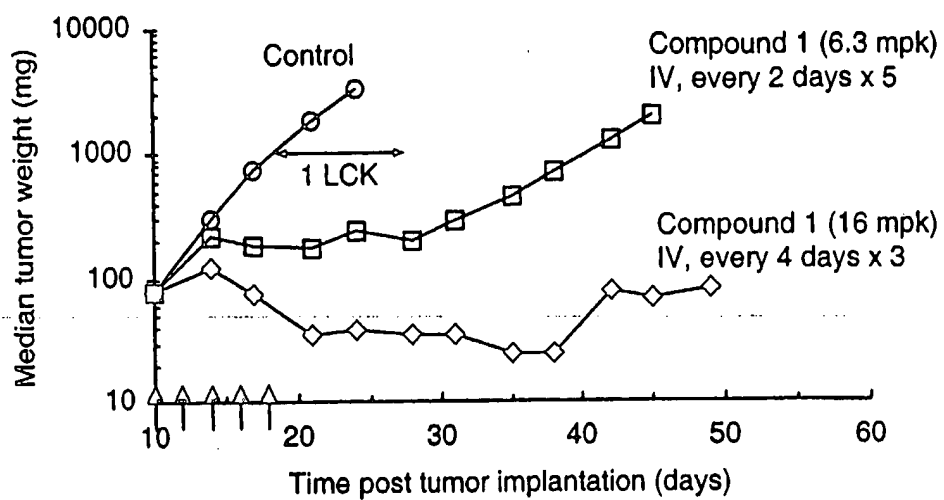


Figure 6

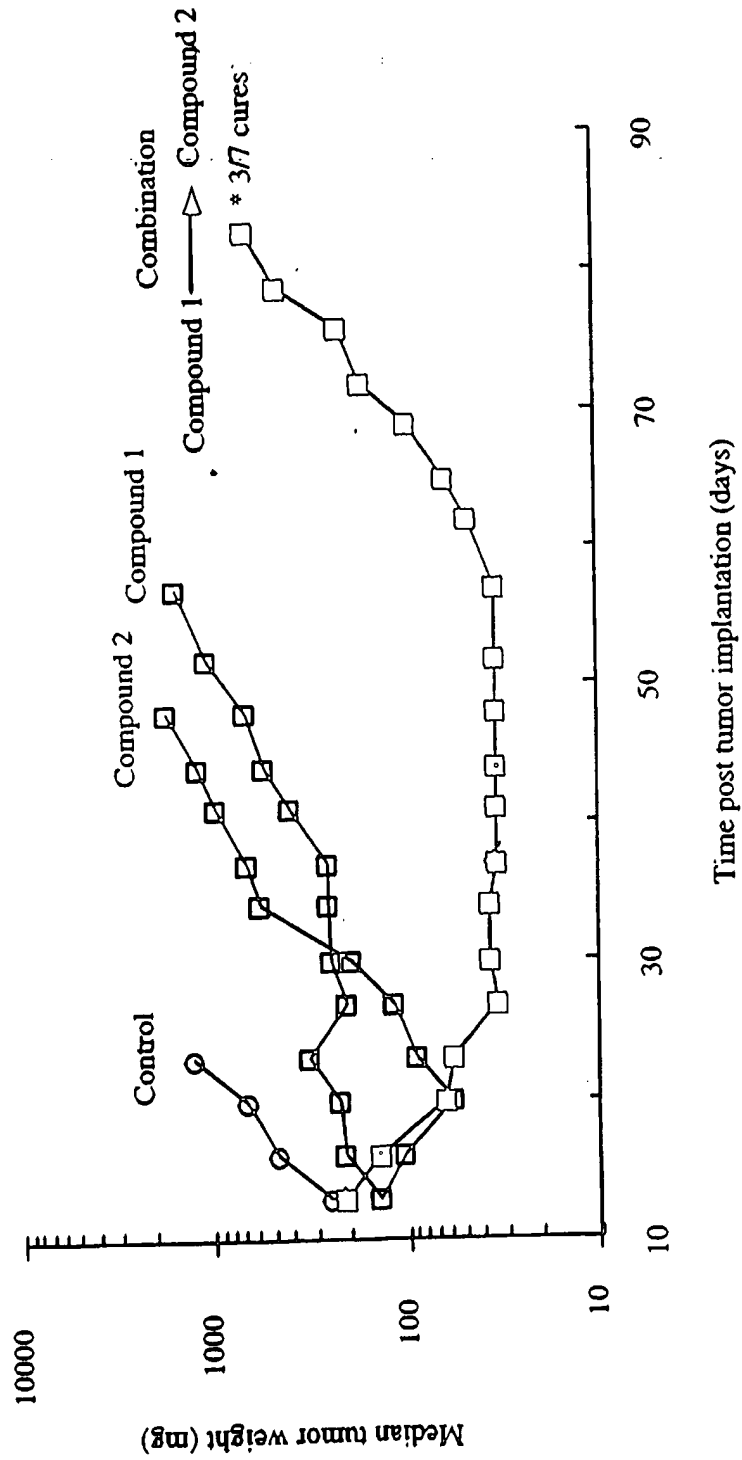


Fig. 7

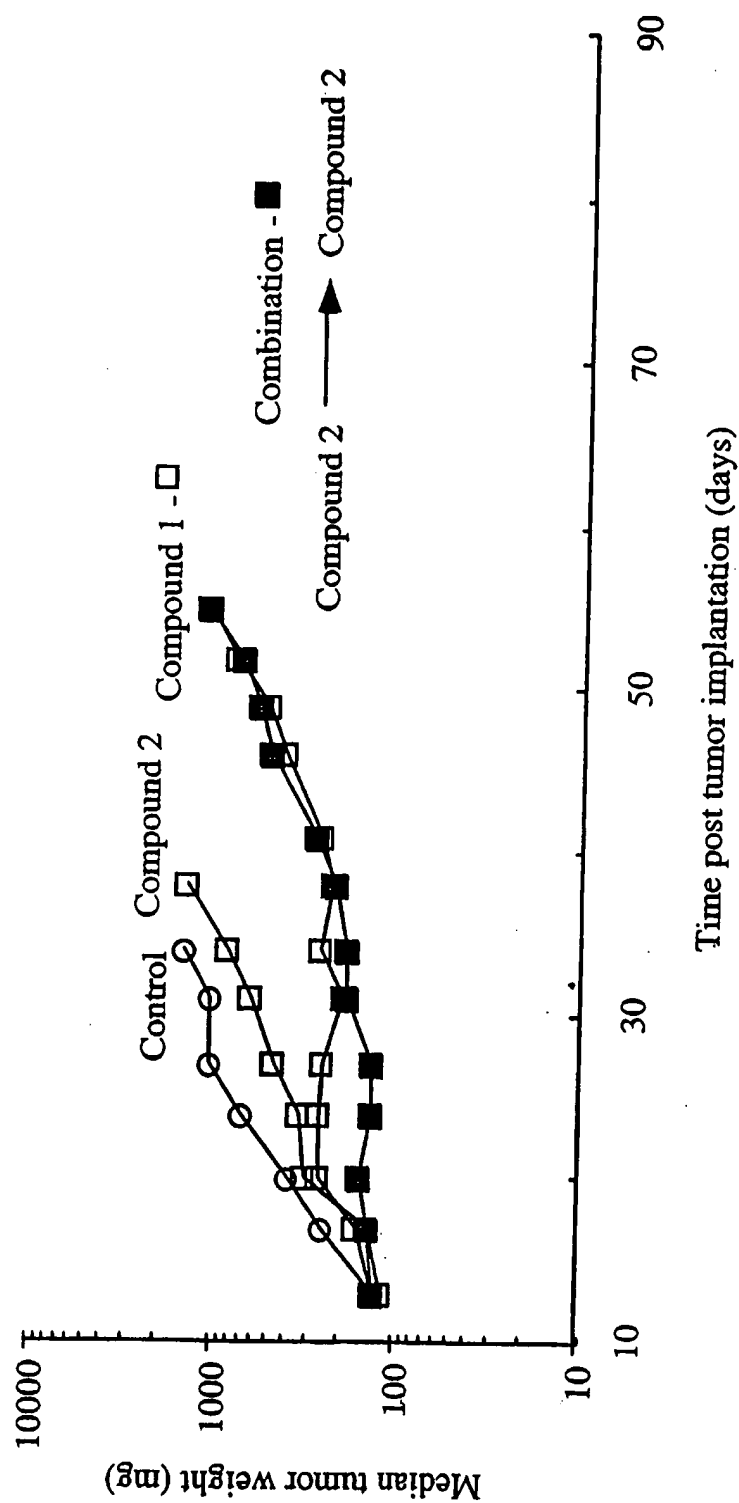


Fig. 8

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## A. CLASSIFICATION OF SUBJECT MATTER

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## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
USPATFULL PCTFULL WPIDS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/02514 A2 (BRISTOL-MYERS SQUIBB COMPANY) 21 January 1999 (21.01.1999), abstract, page 1 lines 10-21, page 2-3, Examples 1-8, claims 1-6	1-70

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WO 02/072085 A3

(54) Title: GLYCYRRHETINIC ACID DERIVATIVES, PROGESTERONE AND PROGESTERONE DERIVATIVES  
AND THEIR USE FOR THE MANUFACTURE OF A MEDICAMENT TO INHIBIT 11BETA-HYDROXYSTEROID  
DEHYDROGENASE ACTIVITY

(57) Abstract: The present invention provides use of a compound in the manufacture of a medicament to inhibit 11 $\beta$ -HSD activity,  
wherein the compound is selected from glycyrrhetic acid derivatives, progesterone and progesterone derivatives.

## INTERNATIONAL SEARCH REPORT

Int lonal Application No

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## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/19 A61K31/215 A61P5/38 A61P5/44 A61P5/46  
 C07C62/32 C07C62/34 C07C62/38 C07C69/753 C07C69/757  
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## B. FIELDS SEARCHED

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MEDLINE, EPO-Internal, CHEM ABS Data, WPI Data, PAJ, BIOSIS, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>BÜHLER H ET AL: "Inhibition of rat renal 11 beta-hydroxysteroid dehydrogenase by steroidal compounds and triterpenoids; structure/function relationship."            BIOCHIMICA ET BIOPHYSICA ACTA. NETHERLANDS            31 OCT 1991,            vol. 1075, no. 3,            31 October 1991 (1991-10-31), pages            206-212, XP001080642            ISSN: 0006-3002            abstract            page 206, right-hand column, paragraph 3            -page 207, left-hand column, paragraph 2            page 207, left-hand column, last paragraph            page 207, right-hand column, 'results',            (A)            table 1, 'compound A'            figure 4</p> <p style="text-align: center;">-/--</p>	<p>1-11,            13-15,            18-22,            24, 26,            28-30,            33-37</p>

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## INTERNATIONAL SEARCH REPORT

tional Application No

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## A. CLASSIFICATION OF SUBJECT MATTER

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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>'discussion' page 211, right-hand column, paragraph 3 ---</p> <p>AKAO T ET AL: "Inhibitory effects of glycyrrhetic acid derivatives on 11 beta- and 3 alpha-hydroxysteroid dehydrogenases of rat liver." CHEMICAL &amp; PHARMACEUTICAL BULLETIN. JAPAN NOV 1992, vol. 40, no. 11, November 1992 (1992-11), pages 3021-3024, XP001080148 ISSN: 0009-2363 abstract the whole document ---</p> <p style="text-align: center;">-/--</p>	<p>1-11, 13-15, 18-22, 24,26, 28-30, 33-37</p>

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Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 02/01060

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 97 07789 A (UNIV EDINBURGH ;WALKER BRIAN ROBERT (GB); EDWARDS CHRISTOPHER RICH) 6 March 1997 (1997-03-06)</p> <p>page 5, line 17 -page 6, line 5 abstract</p>	<p>1-11, 13-15, 18-22, 24,26, 28-30, 33-37</p>
X	<p>STEWART P M ET AL: "11BETA-HYDROXYSTEROID DEHYDROGENASE" VITAMINS AND HORMONES, ACADEMIC PRESS, NEW YORK, NY,, US, vol. 57, 1999, pages 249-324, XP001004592 ISSN: 0083-6729 page 265, paragraph 3 -page 269, paragraph 1 page 298, paragraph 6 -page 290, paragraph 1</p>	<p>1-37</p>
X	<p>US 4 448 788 A (TOYOSHIMA SHIGESHI ET AL) 15 May 1984 (1984-05-15)</p> <p>formulas I and II abstract</p>	<p>1-11, 13-15, 18-22, 24,26, 28-30, 33-37</p>
X	<p>DUAN H ET AL: "Triterpenoids from Tripterygium wilfordii" PHYTOCHEMISTRY, PERGAMON PRESS, GB, vol. 53, no. 7, 1 April 2000 (2000-04-01), pages 805-810, XP004291375 ISSN: 0031-9422 abstract page 805, left-hand column, paragraph 1 compound 15</p>	<p>1-11, 13-15, 18-22, 24,26, 28-30, 33-37</p>
X	<p>US 4 173 648 A (FARINA CARLO ET AL) 6 November 1979 (1979-11-06) formula II column 3, line 45 - line 49</p>	<p>28,33,34</p>
X	<p>SUN, DI-AN ET AL: "DNA Polymerase.beta. Inhibitors from Sandoricum koetjape" JOURNAL OF NATURAL PRODUCTS (1999), 62(8), 1110-1113 , XP002201254 compounds 1, 2, 5, 6, 7, 8 and 10</p>	<p>28,33,34</p>
	-/--	

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 02/01060

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TAKAISHI Y ET AL: "Triterpenoid inhibitors of interleukin-1 secretion and tumour-promotion from Tripterygium wilfordii var. regelii" PHYTOCHEMISTRY, PERGAMON PRESS, GB, vol. 45, no. 5, July 1997 (1997-07), pages 969-974, XP004293236 ISSN: 0031-9422 compounds 10 and 11 ---	28,33,34
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KONDRATENKO, R. M. ET AL: "Synthesis and antiulcer activity of 3-O-acylated glycyrrhetic acid methylates" retrieved from STN Database accession no. 136:247713 XP002201255 abstract & PHARMACEUTICAL CHEMISTRY JOURNAL (TRANSLATION OF KHIMIKO-FARMATSEVTICHESKII ZHURNAL) (2001), 35(5), 243-246 , ---	28-30, 33,34
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KHAKSA, G. ET AL: "Antiinflammatory and antinociceptive activity of disodium glycyrrhetic acid hemiphthalate" retrieved from STN Database accession no. 125:292578 XP002201256 abstract & PLANTA MED. (1996), 62(4), 326-328 , ---	28-30, 33,34
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; YANO, SHINGO ET AL: "Antiulcer activities of glycyrrhetic acid derivatives in experimental gastric lesion models" retrieved from STN Database accession no. 112:16107 XP002201257 abstract & CHEM. PHARM. BULL. (1989), 37(9), 2500-4 --- -/--	28-30, 33,34

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In International Application No

PCT/GB 02/01060

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CA 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            SHIBATA, S.: "Medicinal chemistry of            triterpenoid saponins and sapogenins"            retrieved from STN            Database accession no. 95:73516            XP002201258            abstract            &amp; PROC. ASIAN SYMP. MED. PLANTS SPICES,            4TH (1981), MEETING DATE 1980, VOLUME 1,            59-70. EDITOR(S): KUSAMRAN,            KOSAN;POHMAKOTR, MANAT; REUTRAKUL, VICHAI.            PUBLISHER: AKSORN CHAROEN - TAT PUBL.            HOUSE, BANGKOK, THAILAND. ,</p>	28-30, 33,34
X	<p>-----            PINDUCCIU, G.; SERRA, C.; CAGETTI, M.G.;            COTTI, M.; DEIDDA, D.; PINZA, M.; POMPEI,            R.: "Selective Antibacterial Activity of            Triterpene Derivatives"            MED. MICROBIOL. LETT.,            vol. 4, no. 2, 1995, pages 83-90,            XP001098298            the whole document            abstract            page 84, line 3 - line 4            page 90, line 3 - line 5            table 1</p>	1-11, 13-15, 18-30, 33-37
X	<p>-----            PELLEGATA, R.; PINZA, M.; PIFFERI, G.;            FARINA, C.: "A new reduction of the            Enone-System of 18-beta-Glycyrrhetic Acid"            ORGANIC PREPARATIONS AND PROCEDURES INT.,            vol. 31, no. 2, 1999, pages 181-187,            XP001098252            compounds 8a-8f</p>	28
X	<p>-----            GB 1 570 394 A (GLAXO LAB LTD)            2 July 1980 (1980-07-02)              the whole document            page 1, right-hand column, line 90 -page            2, left-hand column, line 2            p. 3, formula I            page 10, right-hand column, line 60 - line            82              -----            -/--</p>	1-7,12, 16-27, 31-37

## INTERNATIONAL SEARCH REPORT

 International Application No  
 PCT/GB 02/01060

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>LATIF S A ET AL: "Selective inhibition of sheep kidney 11beta-hydroxysteroid dehydrogenase isoform 2 activity by 5alpha-reduced (but not 5beta) derivatives of adrenocorticosteroids"</p> <p>STERIODS: STRUCTURE, FUNCTION, AND REGULATION, ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, US,</p> <p>vol. 62, no. 2,</p> <p>1 February 1997 (1997-02-01), pages 230-237, XP004056328</p> <p>ISSN: 0039-128X</p> <p>abstract</p> <p>page 231, left-hand column, paragraph 2 - paragraph 3</p> <p>table 1</p>	<p>1-7,12,</p> <p>16-27,</p> <p>31-37</p>
X	<p>PHILLIPPS G H ET AL: "WATER-SOLUBLE STEROIDAL ANAESTHETICS"</p> <p>JOURNAL OF STEROID BIOCHEMISTRY, PERGAMON PRESS PLC, GB,</p> <p>vol. 11, no. 1A, 1 July 1979 (1979-07-01), pages 79-86, XP000600717</p> <p>ISSN: 0022-4731</p> <p>compounds of formula I</p>	<p>31,33</p>
A	<p>HULT M ET AL: "Selective inhibition of human type 1 11beta-hydroxysteroid dehydrogenase by synthetic steroids and xenobiotics"</p> <p>FEBS LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL,</p> <p>vol. 441, no. 1,</p> <p>11 December 1998 (1998-12-11), pages 25-28, XP004258864</p> <p>ISSN: 0014-5793</p> <p>abstract</p> <p>table 3</p> <p>page 27, left-hand column, paragraph 2</p> <p>page 27, right-hand column, paragraph 3</p>	<p>1-7,12,</p> <p>16-27,</p> <p>31-37</p>
A	<p>WU P ET AL: "Effects of cholic acid on blood pressure and production of vascular aldosterone and corticosterone - Implications for the pathophysiology of hypertension"</p> <p>STERIODS: STRUCTURE, FUNCTION, AND REGULATION, ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, US,</p> <p>vol. 64, no. 4, April 1999 (1999-04), pages 291-295, XP004172206</p> <p>ISSN: 0039-128X</p> <p>abstract</p> <p>page 293, paragraph 3 -page 294, paragraph 1</p>	<p>1-7,12,</p> <p>16-27,</p> <p>31-37</p>

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB 02/01060

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

## 1. Invention:

Present claims 1-11, 13-15, 18-22, 24, 26, 28-30, 33-37 relate to an extremely large number of possible compounds that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds having residues as recited in the examples.

This means that the search has been restricted to compounds of formula II where R1 is limited to -O-, R5, R6, R7, R11 and R12 is -CH3, R8 and R9 are -CH3 or -H and R10 is -O- or -N-, and C12-C13 is a single or double bond.

## 2. Invention:

Present claims 1-7, 12, 16-22, 24, 26, 36 and 37 relate to an extremely large number of possible compounds that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been limited to the compounds defined in claim 31 and to 'progesterone-derivatives' in general.

The compounds given as examples could not be included in the search as having (a) double bond(s), contrary to the compounds defined within the claims, which would result in the retrieval of an extremely large number of steroids.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-7 (partially), 8-11, 13-15 (partially),  
18-27 (partially), 28-30, 33-37 (partially)

Subject 1 of the present application relates to the provision of glycyrrhetic acid derivatives (see formulas I and II) and their use for the manufacture of a medicament for the inhibition of 11beta-hydroxysteroid dehydrogenase (11beta-HSD).

2. Claims: 1-7 (partially), 12, 16, 17, 18-27 (partially), 31,  
32, 33-37 (partially)

Subject 2 of the present application relates to the provision of progesterone and derivatives thereof (see formulas I and III) and their use for the manufacture of a medicament for the inhibition of 11beta-hydroxysteroid dehydrogenase (11beta-HSD).

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 02/01060

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9707789	A	06-03-1997	AU 6833796 A	19-03-1997
			EP 0847275 A1	17-06-1998
			WO 9707789 A1	06-03-1997
			GB 2317826 A ,B	08-04-1998
			US 2001039294 A1	08-11-2001
			US 2002076781 A1	20-06-2002
US 4448788	A	15-05-1984	JP 1048254 B	18-10-1989
			JP 1569323 C	10-07-1990
			JP 58008044 A	18-01-1983
			AT 13523 T	15-06-1985
			DE 3263882 D1	04-07-1985
			EP 0069380 A1	12-01-1983
US 4173648	A	06-11-1979	IT 1075675 B	22-04-1985
			AR 218294 A1	30-05-1980
			AT 361640 B	25-03-1981
			AT 183078 A	15-08-1980
			BE 864892 A1	14-09-1978
			CA 1102304 A1	02-06-1981
			CH 640502 A5	13-01-1984
			DE 2811253 A1	21-09-1978
			ES 467886 A1	01-11-1978
			FR 2383909 A1	13-10-1978
			GB 1575494 A	24-09-1980
			JP 1449021 C	11-07-1988
			JP 53116363 A	11-10-1978
			JP 62059099 B	09-12-1987
			MX 4989 E	31-01-1983
			NL 7802881 A ,B,	19-09-1978
			PT 67783 A	01-04-1978
			YU 61878 A1	21-01-1983
GB 1570394	A	02-07-1980	AU 513579 B2	11-12-1980
			AU 2106577 A	13-07-1978
			BE 850108 A1	05-07-1977
			CA 1084903 A1	02-09-1980
			DE 2700267 A1	14-07-1977
			DK 3577 A	07-07-1977
			FR 2361419 A1	10-03-1978
			JP 52085159 A	15-07-1977
			NL 7700054 A	08-07-1977
			NZ 183004 A	05-03-1980
			SE 7700098 A	07-07-1977
			US 4192871 A	11-03-1980
			ZA 7700059 A	22-02-1978